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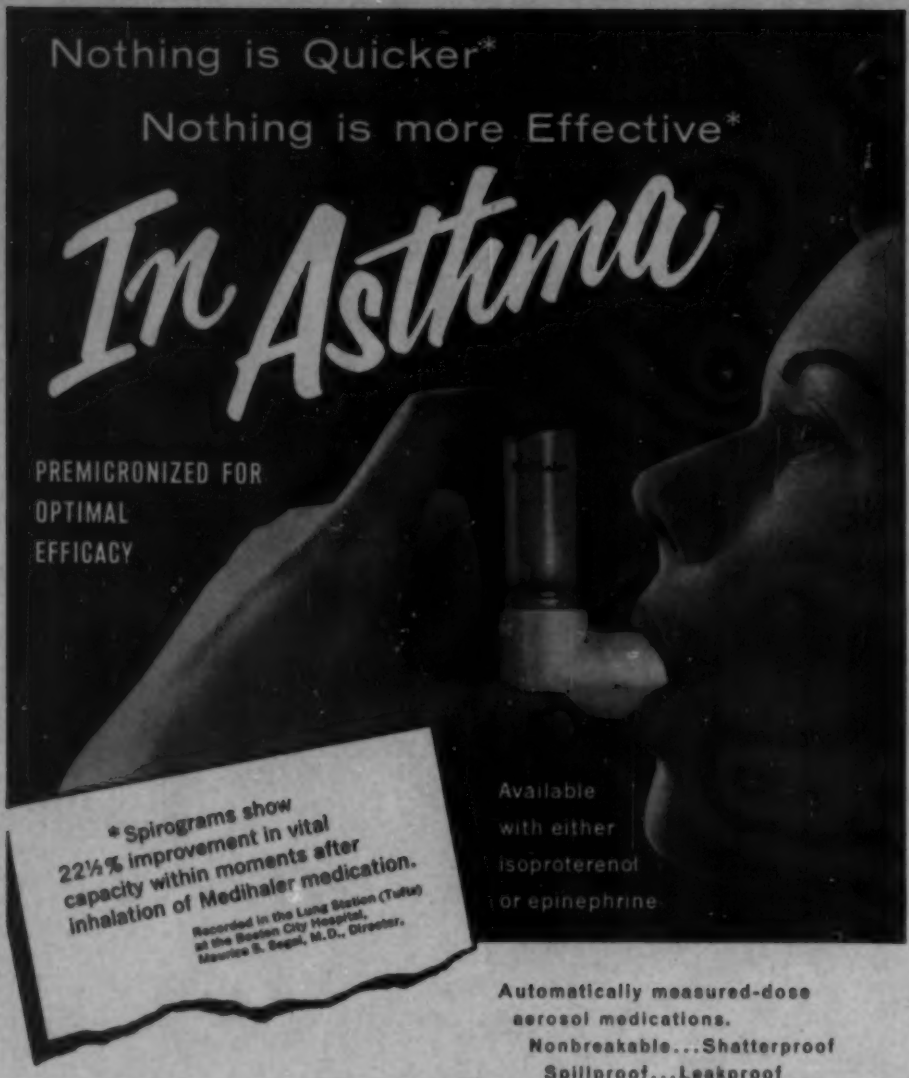
VOLUME XXXVI • NUMBER 5
NOVEMBER 1959

DISEASES of the CHEST

OFFICIAL PUBLICATION

Silver Anniversary Year

Interim Session
Dallas, Texas, November 29-30, 1959



Automatically measured-dose aerosol medications.
Nonbreakable...Shatterproof
Spillproof...Leakproof

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Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

Medihaler–EPI®

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

NOTABLY WELL TOLERATED AND EFFECTIVE FOR CHILDREN, TOO

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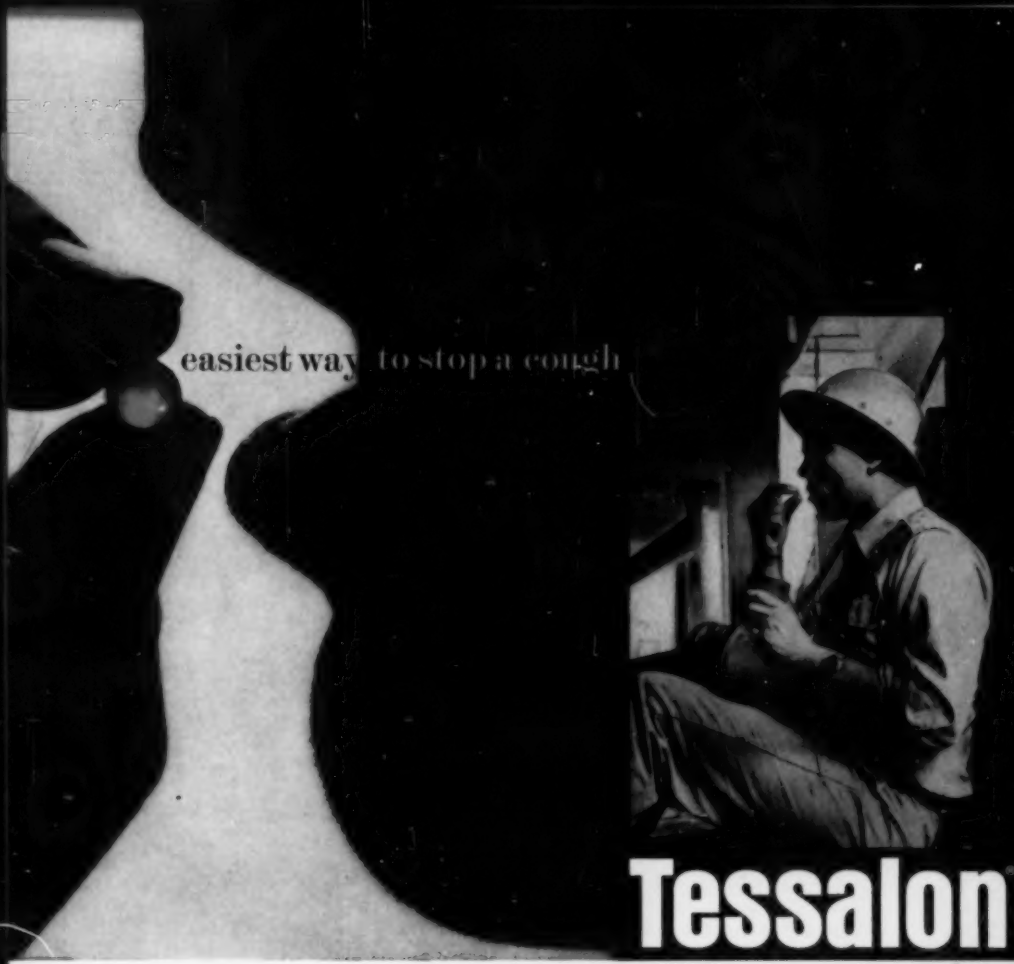


Tessalon®

perles

Tessalon perles stop cough fast—and they're convenient to take. No mess, no spillage, no awkward spoons or bottles to carry around. Another advantage: *no taste*. An exact, effective dose is sealed in a tiny gelatin sphere.

Reasons *why* Tessalon stops cough so effectively: it acts where cough begins—in the chest; it acts at the cough reflex center—in the medulla; it acts promptly—within 15 to 20 minutes, the effect lasting up to 8 hours. Tessalon is *not* a narcotic, yet has been reported 2½ times more effective than codeine in suppressing cough.[1]

SUPPLIED: Tessalon *Perles*, 100 mg. (yellow); bottles of 100. Tessalon *Pediatric Perles* (for children under 10), 50 mg. (red); bottles of 100. *Also available* (for use when oral administration of Tessalon is precluded): *Ampuls*, 1 ml. (5 mg.); cartons of 5.

1. Shane, S. J., Krzyski, T. K., and Copp, S. E.: Canad. M. A. J. 77:500 (Sept. 15) 1957.

Remember
SERPASIL®
(reserpine CIBA)
for the anxious hypertensive with or without tachycardia

a/ctessx TESSALON® (benzonatate CIBA)

CIBA
Summit, New Jersey

DISEASES *of the* CHEST

OFFICIAL PUBLICATION

OF THE

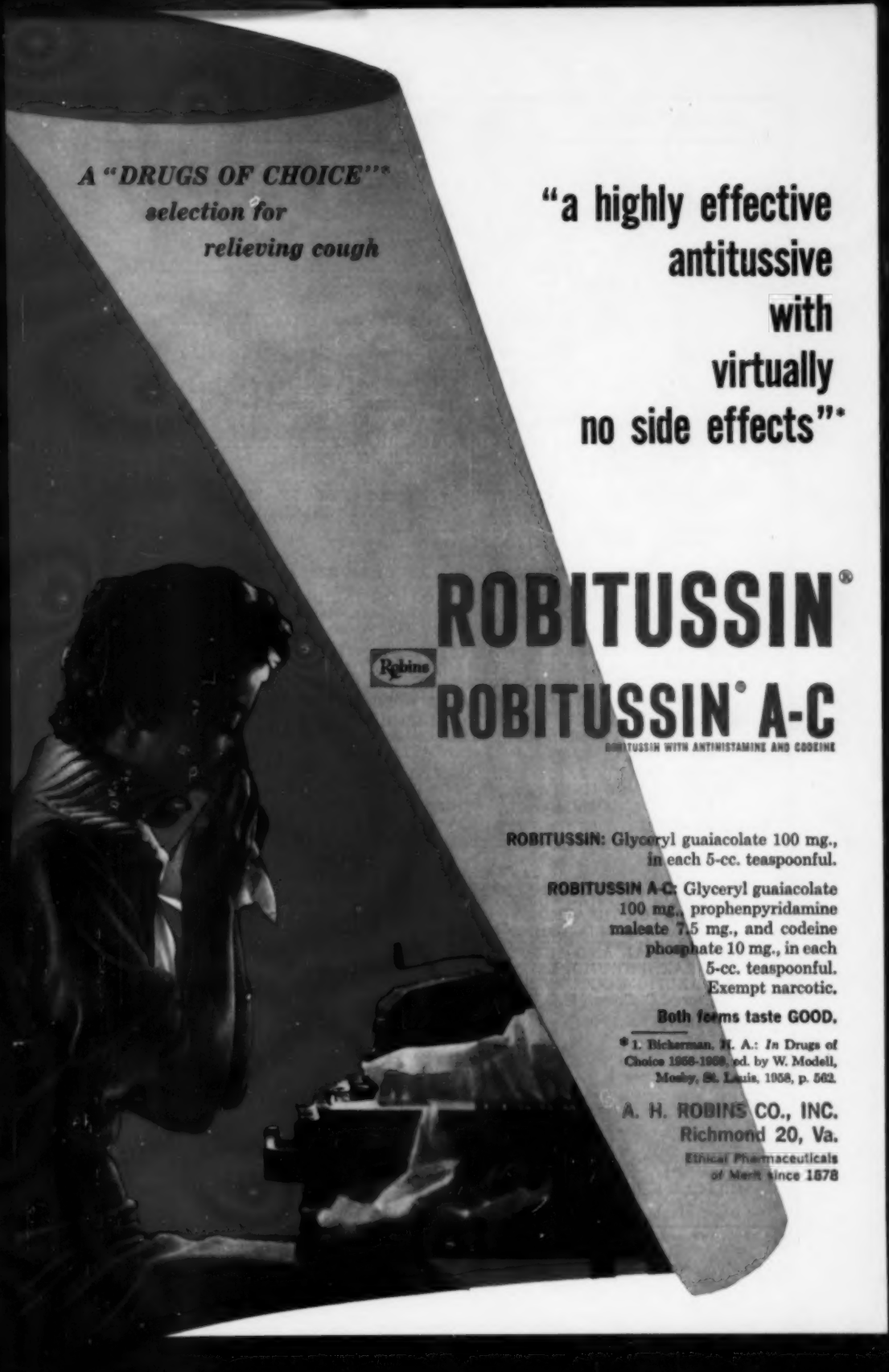
AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE

112 East Chestnut Street, Chicago 11, Illinois, U.S.A.

MURRAY KORNFELD, *Managing Editor*

WARD BENTLEY, *Publication Manager*


A "DRUGS OF CHOICE"*
selection for
relieving cough
"a highly effective
antitussive
with
virtually
no side effects"*
ROBITUSSIN®
Robins
ROBITUSSIN® A-C
ROBITUSSIN WITH ANTIHISTAMINE AND CODEINE
ROBITUSSIN: Glyceryl guaiacolate 100 mg., in each 5-cc. teaspoonful.
ROBITUSSIN A-C: Glyceryl guaiacolate 100 mg., prophenpyridamine maleate 7.5 mg., and codeine phosphate 10 mg., in each 5-cc. teaspoonful. Exempt narcotic.
Both forms taste GOOD.
* 1. Bicherman, H. A.: In Drugs of Choice 1958-1959, ed. by W. Modell, Mosby, St. Louis, 1958, p. 562.
A. H. ROBINS CO., INC.
Richmond 20, Va.
Ethical Pharmaceuticals
of Merit since 1878

VOLUME XXXVI NOVEMBER, 1959 NUMBER 5

CONTENTS

SECTION ON CARDIOVASCULAR DISEASES

CASE REPORT SECTION

Second Class Postage Paid at Chicago, Illinois

Annual Subscription: $15.00, postpaid to any part of the world

for the tense and nervous patient

relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*—400 mg. *unmarked,* coated tablets.

Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES / *New Brunswick, N. J.*

CM-6204

LEDERLE INTRODUCES...

a masterpiece

greater antibiotic activity

Milligram for Milligram, DECLOMYCIN exhibits 2 to 4 times the activity of tetracycline against susceptible organisms. (*Activity* level is the basis of comparison—not quantitative blood levels—since action upon pathogens is the ultimate value.*) Provides significantly higher serum activity level . . .

with far less antibiotic intake

DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

unrelenting peak antimicrobial attack

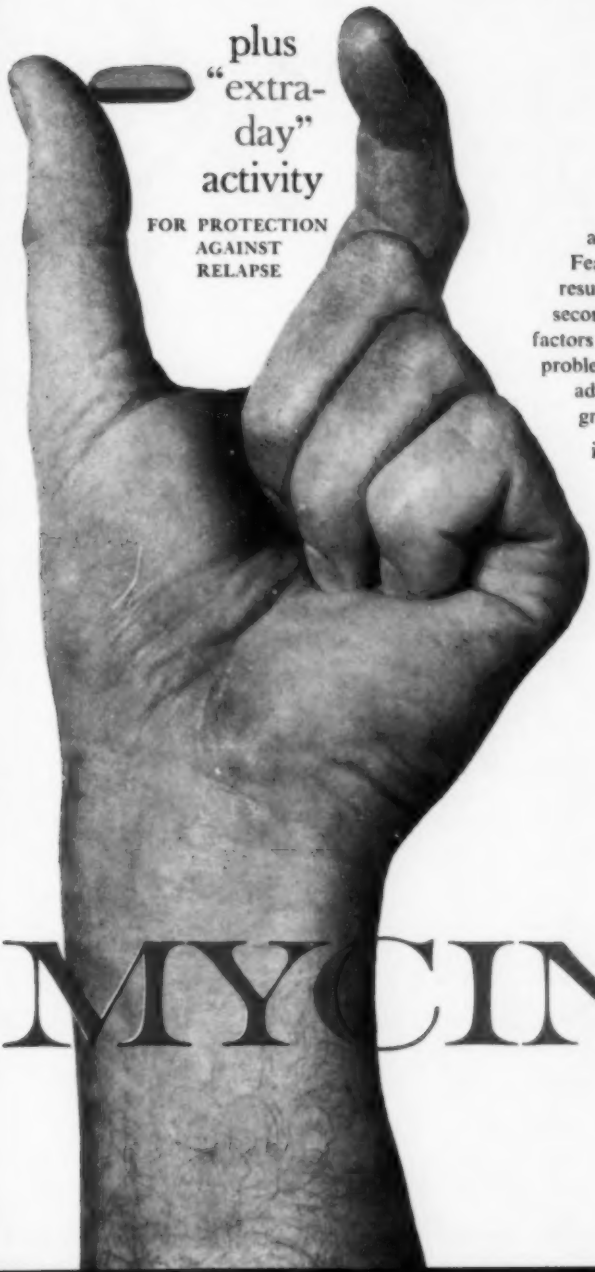
The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

DECLO

Demethylchlortetracycline Lederle

# of antibiotic design



plus "extra-day" activity

FOR PROTECTION AGAINST RELAPSE

DECLOMYCIN maintains activity for one to two days after discontinuance of dosage. Features unusual security against resurgence of primary infection or secondary bacterial invasion—two factors often resembling a "resistance problem"—enhancing the traditional advantages of tetracycline... for greater physician-patient benefit

in the distinctive, dry-filled, duotone capsule

immediately available as:
DECLOMYCIN
Capsules, 150 mg.,
bottles of 16 and 100.
Adult dosage: 1 capsule
four times daily.

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a Division of
AMERICAN CYANAMID COMPANY
Pearl River, New York

The CHASE
CATHETERIZING BRONCHOSCOPE

An Instrument for Catheterizing Upper Lobe Bronchi and for other Bronchoscopic Procedures

The instrument consists of an 8 mm tube, an oxygen inlet tube and a suction tube. A light carrier permits the use of the instrument as a standard bronchoscope.

The light carrier channel is used to convey the catheter and a permanent deflecting mechanism in the distal end deflects the catheter in a right angle direction.

A right angle telescope, used with a removable adapter, is necessary for visualization of the bronchus to be catheterized.

The Broyles Right Angle Telescope, Cat. No. 4703, can be used with the Chase Catheterizing Bronchoscope, but is not supplied as a part of the instrument.

Cat. No. 4690

The Chase Catheterizing Bronchoscope can be used for

- Regular bronchoscopy.
- Catheterization of an inflamed bronchus and do a bronchial lavage for sputum near the lesion.
- Location of strictures from swelling of bronchi and reduction of swelling by application of neo-synephrine to reduce or collapse the swollen cavity.
- Sectional bronchography.
- Drainage of some lung abscesses.

ESTABLISHED IN 1900 BY REINHOLD WAPPLER

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American Cystoscope Makers, Inc.

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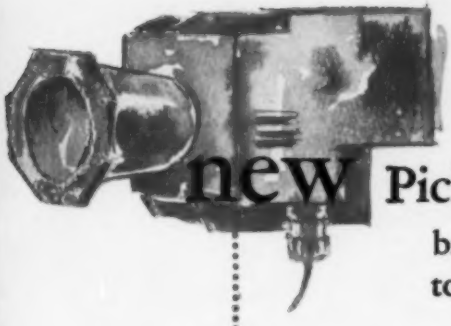


new Picker Minograph camera

brings new performance standards to TB case-finding photofluorography

what's new about it?

Plenty.....

It's ***the first camera*** specifically designed (not merely adapted) to fully exploit the speed and definition of a great f0.95 lens. Its 120 mm focal length is ideal for 70 mm film coverage.

It's ***better than twice as fast*** as a conventional f1.5 photofluorographic camera lens: reduces subject irradiation by more than one-half.

It ***retains the compactness,*** reliability and proven stamina of a lens type camera. No need to coddle it: takes the hard knocks of field survey work in stride.

Its ***vacuumized film platen*** takes the curl out, holds film board-flat during exposure: enhances image detail.

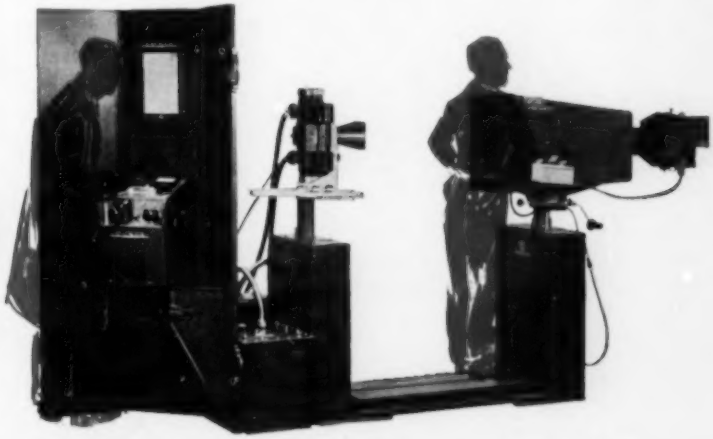
Its ***separable piggyback magazine*** and built-in guillotine lets you sever and develop exposed film lengths without removing the main magazine.

It's ***readily substituted*** for existing cameras in older Picker Minographs.

It's ***another reason why,*** when it comes to equipment for photofluorography, your local Picker man is the man to see.

Picker x-ray

PICKER X-RAY CORPORATION
25 South Broadway, White Plains, N. Y.



The Picker Minograph *field-proven the world over in TB survey work.*

NEW PERMITIL®

FLUPHENAZINE DIHYDROCHLORIDE

the promise of

in everyday practice:

Safely controls the "target symptoms" of emotional stress with the smallest effective dosage of any neuroleptic* agent (0.25 mg. b.i.d.)

**neuroleptic*

"The term 'neuroleptic' implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on affective tension that distinguishes this response from that to hypnotic drugs. The terms 'ataraxics' and 'tranquilizers' are descriptively impressive, but fail to convey what seems psychopharmacologically unique."[1]

PERMITIL

to fit the promise to your practice

***The Major Advantages of* PERMITIL:**

■ *Unusually safe, fractional milligram dosage.* Made possible by PERMITIL's greatly enhanced activity[1], rapid onset and prolonged duration of action.

■ *Unparalleled freedom from depressant effects.* Many of the annoying side effects of the other phenothiazines, which are dosage-related, occur less frequently or not at all with PERMITIL. Thus PERMITIL alleviates symptoms of anxiety *without* producing drowsiness, impaired alertness or slowed intellectual function.

■ *Expanded spectrum of "target symptoms".* Anxiety-induced symptoms of apathy, reduced initiative and chronic emotional fatigue—often refractory to other phenothiazines—frequently respond to PERMITIL. The patient regains a more confident outlook and normal drive is restored.

***The Areas of Usefulness for* PERMITIL:**

■ Behavioral disturbances characterized by anxiety, tension, apprehension and instability, as well as depressive symptoms associated with anxiety states.

■ Emotional stress accompanying organic disorders and complicating recovery from, or acceptance of, the underlying condition.

■ Chronic disorders in which anxiety and stress are contributing factors, e.g., gastrointestinal dysfunctions, neurodermatitis, asthma, premenstrual tension, arthritis, hypertension and tension headache.

***How to Prescribe* PERMITIL:**

The recommended dose for most adults is one 0.25 mg. tablet twice a day. This may be increased to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms who have had a trial of lower dosages first that were well tolerated but were only partially effective. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. (Dosage for children has not been established.)

Side Effects—Infrequent; Contraindications—Minimal.

At the recommended dosage of PERMITIL, side effects have been observed infrequently or not at all. PERMITIL, as with other phenothiazines, is contraindicated in severely depressed states.

Available in Tablets of 0.25 mg.; bottles of 50 and 500.

References: 1. Freyhan, F. A.: Psychopharmacology Frontiers, Boston, Little, Brown & Co., 1959, p. 7. 2. Ayd, F. J.: The current status of major tranquilizers, in press.

WHITE LABORATORIES, INC., *Kenilworth, New Jersey*

PROVEN EFFECTIVE FOR THE TENSE AND NERVOUS PATIENT

"There is perhaps no other drug introduced in recent years which has had such a broad spectrum of clinical application as has meprobamate.* As a tranquilizer, without an autonomic component in its action, and with a minimum of side effects, meprobamate has met a clinical need in anxiety states and many organic diseases with a tension component."

Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

Miltown®

the original meprobamate, discovered and introduced by

WALLACE LABORATORIES, *New Brunswick, N. J.*

CM-213

For the first time

CONVENIENCE and ECONOMY

for that all-important first dose of broad-spectrum antibiotic therapy

New

TERRAMYCIN®

oxytetracycline

INTRAMUSCULAR SOLUTION

Initiation of therapy in **minutes after diagnosis** with new, ready-to-inject Terramycin Intramuscular Solution provides maximum, sustained absorption of potent broad-spectrum activity.

...and for continued, compatible, coordinated therapy

COSA-TERRAMYCIN®

oxytetracycline with glucosamine

CAPSULES

Continuation with oral Cosa-Terramycin every six hours will provide highly effective antibacterial serum and tissue levels for prompt infection control.

The unsurpassed record of clinical effectiveness and safety established for Terramycin is your guide to successful antibiotic therapy.

Supply:

Terramycin Intramuscular Solution*
100 mg./2 cc. ampules 250 mg./2 cc. ampules

Cosa-Terramycin Capsules
125 mg. and 250 mg.

Cosa-Terramycin is also available as:

Cosa-Terramycin Oral Suspension – peach flavored.
125 mg./5 cc., 2 oz. bottle

Cosa-Terramycin Pediatric Drops – peach flavored.
5 mg./drop (100 mg./cc.), 10 cc. bottle with plastic calibrated dropper

Complete information on Terramycin Intramuscular Solution and Cosa-Terramycin oral forms is available through your Pfizer Representative or the Medical Department, Pfizer Laboratories.

*Contains 2% Xylocaine® (lidocaine), trademark of Astra Pharmaceutical Products, Inc.

Pfizer *Science for the world's well-being™*

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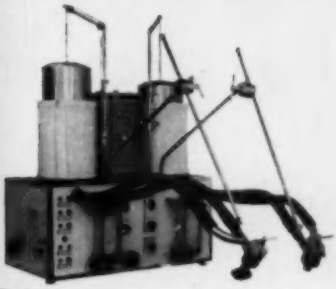
PULMONARY-FUNCTION EQUIPMENT

GODART PULMOTEST

The universal double spirometer, the most compact versatile lung function station for determination of lung volumes and its subdivisions. Maximum breathing capacity, timed vital capacity, and oxygen consumption at rest or in exercise can be determined. The GODART PULMOTEST enables the subject to breathe room air, oxygen being added as it is used, maintaining starting concentration, 3-speed kymograph, motor blower, volume integrator, suitable for closed circuit residual volume determination in conjunction with the PULMO-ANALYSOR.



GODART PULMO-ANALYSOR

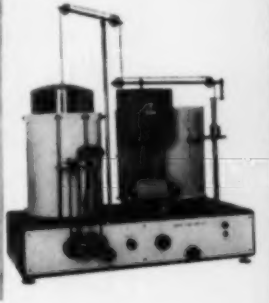
The PULMO-ANALYSOR is a highly accurate thermal conductivity gas analysor which is sensitive to He, CO_2 and O_2. Usable alone and in conjunction with the GODART PULMOTEST, it can be used to determine residual volume by closed circuit helium method as well as by the open circuit method. Expired gas analysis for O_2 and CO_2 in mixtures with the highest accuracy, speed and precision.

CAPNOGRAPH

This infra-red gas analysor is used for recording dynamic changes in the level of CO_2 in respiration. The response time is rapid (.04 sec.) and is able to follow the respiratory cycle. Alveolar CO_2 values are obtainable without recourse to sampling devices. Capacity is highly stable and accurate to 0.1% of its measuring range, compact and ready for immediate use in proper control of artificial respiration, determination of dead space volume, diagnosis of emphysema, chronic hyperventilation.

GODART COMPLIANCE TEST

To study the elastic properties of the lungs. This equipment records as a kymograph, a loop representing the relation between pressure and volume during respiration. Intra-esophageal pressure changes are detected from a catheter by an electromanometer, volume changes by a precision spirometer and fed into special recorder type kymograph. Supplied with an electromanometer, 3-speed kymograph and all accessories.



GODART DESIGNED PULMONARY FUNCTION APPARATUS

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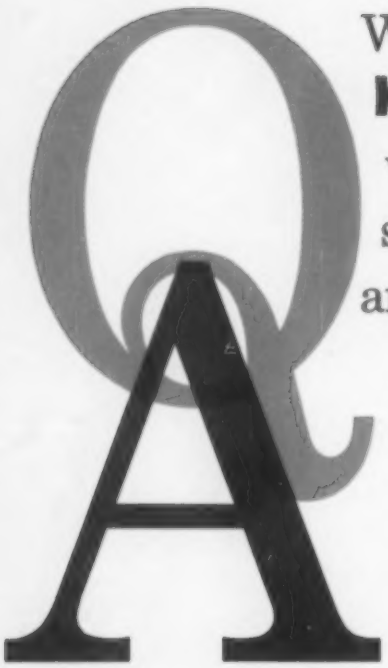

Why should I use **KANTREX**® Injection* when there are so many other antibiotics available?

Because KANTREX Injection is bactericidal to a wide variety of organisms, including many that are highly resistant to the other antibiotics[3,4,10,12,13,17,18,20,21,23,24,25,27,30,33,35,37]

—organisms such as *Staph. aureus, Staph. albus, A. aerogenes, E. coli, H. pertussis, K. pneumoniae, Neisseria* sp., *Shigella, Salmonella* and many strains of *B. proteus.*

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

Next page, please .....

* Kanamycin sulfate injection (Bristol)

Q *But if I use* KANTREX *Injecti bacteria resistant to it also?*

A A very good question, but it in almost two years of clinica treatment of infections for v the emergence of KANTREX- lations has not been a probl

Q *My impression is that* KANTR *cin. Isn't that so?*

A Indeed not. The only thing have in common is a similar Otherwise, they're very diffe chemical structures; the toxi less than that of neomycin"[14] Injection is practical for syst tinely, while neomycin is no

Q *You mean that* KANTREX *In nephrotoxicity of neomycin?*

A Precisely. It's true that wh used, urinary casts – even sli scopic hematuria – may ap hydrated patients, but this gressive damage to the kidne disappear on adequate hyd therapy.

Q *Then why do you recommer tients with renal impairment*

A Because renal impairment ca lation of KANTREX in the bloo doses are administered. Since creted entirely by the kidney

Injection, won't that help make also?

but it is reassuring to note that clinical use of KANTREX for the s for which it is recommended, NTREX-resistant bacterial popu- problem.

KANTREX is just another neomy-

thing KANTREX and neomycin similar antimicrobial spectrum. y different: they have different he toxicity of KANTREX is "much ycin"[14]; and clinically, KANTREX or systemic administration rou- is not.

REX Injection doesn't have the mycin?

at when KANTREX Injection is ven slight albuminuria or micro- ay appear, especially in poorly t this does not reflect any pro- e kidneys. These signs promptly e hydration or termination of

ommend reduced dosage in pa- rment?

ent causes an excessive accumu- he blood and tissues, when usual . Since KANTREX Injection is ex- kidneys, renal impairment leads to unnecessarily high and prolonged blood levels; and such excessive concentrations increase the risk of ototoxicity.

Q *Is that why we see reports of patients developing hearing loss during* KANTREX *Injection therapy?*

A Yes. A study of the few reported cases in which patients have suffered impaired hearing will show that in every instance they had pre-existing or concurrent renal impairment, yet received usual or excessive doses of KANTREX Injection. Dosage recommendations for KANTREX Injection emphasize that in patients with renal dysfunction, adequate serum levels can be achieved with a fraction of the dose suggested for patients with normal kidney function – with minimal risk of ototoxicity.

Q *Since urinary tract infections are often accompanied by renal impairment, does that mean I shouldn't use* KANTREX *Injection in such conditions?*

A Not at all. With proper precautions, KANTREX Injection is an excellent drug for the treatment of urinary tract infections, especially those due to *Proteus, A. aerogenes* and *E. coli*, even when renal impairment is present.

Q *What are the "proper precautions" in a patient with impaired renal function?*

A The package literature covers them in detail. First, the daily dose should be reduced in such a patient. Then, if he is going to receive KANTREX Injection for 7 days or more, a pre-treatment audiogram should be done, and it should be repeated at appropriate intervals during therapy. If tinnitus or subjective hearing loss develops, or if followup audiograms show significant loss of high frequency response, KANTREX therapy should be discontinued. However, therapy for 7 days or more

is seldom required because the clinical response to KANTREX Injection is so rapid.

Q *Why do you put so much emphasis on* KANTREX'S *"rapid action"? Every antibiotic I've heard about is supposed to be "rapid acting."*

A There is such an abundance of clinical evidence about "rapid acting" that it takes KANTREX Injection out of the "supposed-to" class.[1,2,3,7,8,9,11,15,16,19,21,22,26,29,32,33] Remember, the effectiveness of KANTREX Injection therapy can usually be appraised in 24 to 36 hours. That's definite evidence of rapid action. In fact, one group of investigators reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[29]

Q *Does* KANTREX *Injection cause blood dyscrasias?*

A In extensive clinical and toxicity studies by numerous investigators, as well as almost two years of general use, not a single instance of such toxicity has been reported.

Q *Can I administer* KANTREX *Injection in any other way than by the intramuscular route?*

A Yes. While it's usually given intramuscularly, other routes are practicable: intravenous, intraperitoneal, by aerosol, and as an irrigating solution. Complete instructions are included in the package insert.

Q *So you think I ought to use* KANTREX *Injection as my first choice antibiotic in staph and gram-negative infections?*

A Yes – because all evidence to date indicates that it is bactericidal against a wide range of organisms…rapid acting…does not encourage development of bacterial resistance…is well tolerated in specified dosage…and has not caused any blood dyscrasias.

KANTREX® CAP

for local gastroin
not for systemic i

Q *Why can't I use* KANTREX *Caps*
cation?

A Because there is only negligible a
from the gastrointestinal tract.[3]
cannot provide effective blood l

Q *Then what are* KANTREX *Caps*

A Preoperative bowel sterilizatio
of intestinal infections due t
organisms.

Q *I've been using neomycin for pr*
lization. Why should I switch

A Because KANTREX has been rat
mycin" for this purpose.[6] It pr
factory control of coliforms, cl
and streptococci; yeasts do not
centrations of the drug are e
nausea, vomiting or intestinal i
observed.[5,6]

Q *What advantages do* KANTREX
treatment of intestinal infectio

A A high degree of effectivenes
pathogens responsible for such
Shigella, Staph. aureus, E. co
tolytica. Moreover, their use ha
of any side effects."[31]

CAPSULES

strointestinal therapy...
mic infections

Capsules for systemic medi-

igible absorption of KANTREX
tract.[3,5,6,8,28,34] Thus, capsules
blood levels.

Capsules used for?

lization, and local treatment
due to kanamycin-sensitive

for preoperative bowel steri-
witch to KANTREX Capsules?

en rated as "superior to neo-
" It provides rapid and satis-
rms, clostridia, staphylococci
do not proliferate; stool con-
are exceptionally high; and
tinal irritation have not been

TREX *Capsules offer me in the*
nfections?

iveness against most of the
r such infections: *Salmonella*,
E. coli and *Endamoeba his-*
use has been "remarkably free

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS
Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives"; genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis.

DOSAGE: INTRAMUSCULAR ROUTE
Recommended daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses.

For intramuscular administration, KANTREX Injection should be injected deeply into the upper outer quadrant of the gluteal muscle.

TOXICITY
When the recommended precautions are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of ototoxic reactions is negligible.

In patients with renal disease and impaired renal function, the daily dose of KANTREX should be reduced in proportion to the degree of impairment to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 7 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION
KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS
Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY
Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE
For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

PRECAUTION
Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

SUPPLY
KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

REFERENCES:

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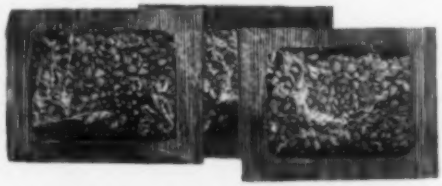

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DISEASES of the CHEST

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Demography of Cancer of the Lung*

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Search for causes of cancer of the lung has been focused on two groups of admittedly responsible factors; intra and extracellular ones. The first group includes: a) hereditary and b) enzymatic, and other factors. The second group includes: a) physical, b) biological and c) chemical agents.

The hereditary factor is well-known from the study of neoplasms in animals. Some strains of laboratory animals are more prone to cancer than others. These strains have been bred for research purposes.

In order to explain the mechanism of transmission of certain biological agents (e.g. viruses) it has been postulated that they act on the chromosomes, bringing about changes in the genes which virtually convert the gene into a gene-virus capable of transmitting mutation through generations. This theory has sought to reconcile the viral and non-viral theories of the origin of cancer.

Enzymatic abnormalities, changes in catalases, oxydases, phosphatases, etc., are factors that seem to accompany rather than cause cancer.

Extracellular factors, trauma, sunlight and other forms of irradiation, and various viruses are also well-known. Rous' chicken-sarcoma, renal carcinoma of the frog (Lucke), Shope's rabbit-carcinoma, and Bittner's milk factor are examples of tumors produced by viruses.

The list of carcinogenic substances is legion. We may recall that Hartwell, cited by Spencer and Herbut[1] in revising 1,028 substances mentioned in the literature listed 284 carcinogenic ones. Among them are a number commonly used by man; petroleum derivatives, such as mineral oil, paraffin, benzene, both natural and synthetic hydrocarbons; furthermore oleic acid, sesame oil, peanut oil, some lards and probably cholesterol. Chronic irritants, tar, soot, tobacco-smoke, radio-active dusts are also well known.

Less known and less extensively studied factors than those included in the intra and extracellular groups are of much interest. They are those which may cause the great variation in the geographical incidence of cancer. Moreover, certain migratory movements reveal differences in the incidence of cancer among natives and immigrants in various countries.

Our studies on the incidence of cancer in Mexico uncovered some facts that coincide with the findings of authors in other countries in regard to the susceptibility of immigrants to cancer of the lung. We also found some

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puzzling communications that caused us to seek an explanation or a theory capable of reconciling their variances and apparent contradictions.

In 1956 D. Eastcott[2] in a paper on Epidemiology of Primary Pulmonary Cancer in New Zealand stated that the mortality from lung cancer was definitely higher among white immigrants from the United Kingdom than among native-born white New Zealanders. Immigrants as a whole had a 30 per cent higher mortality, those arriving in New Zealand at the age of 30 or over had a 75 per cent higher mortality from this disease. The difference existed only for pulmonary cancer but not for other forms of carcinoma. Eastcott concludes that: "immigrants from Great Britain to New Zealand are affected by their former environment and that this effect is related to the length of exposure in that environment. It shows itself in an increase in lung cancer but not in cancer of any other site."[3]

In 1957 J. Rakower[4] in a study of cancer of the lung in Israel, found a striking difference in its incidence among Jews born in Asia and Africa and those migrating from Europe. In the years 1950-54 the death-rates per 100,000 of European immigrants were: 11.2, 10, 11.2, 13.2, and 16.7 while for Asian and African Jews they were 3.1, 1.8, 4.3, 4.5 and 5.1; that is to say, the rates for immigrants were about three times higher than those for mideastern Jews. Rakower also found the mortality among women to be higher in Israel than elsewhere. "This difference may be partially explained by the delay in the adoption of cigarette smoking by Asiatic and African people. However, since mortality from cancer of almost all sites is lower in Asiatic and African immigrants, it may be assumed that there are also other unknown factors responsible for these differences."

In 1957 Buechley, Dunn *et al.*, published a study[5] of cancer of the lung among Mexicans resident in California. They used Spanish surnames as a criterion of nationality. They found an excessive mortality among all Mexican-born women over the age of 45. Their findings agree with those of Steiner.[5-7] Buechley *et al.* say: "A study of lung cancer mortality among the Spanish surname population of California for the period 1949 to 1953 shows a twofold excess among women but not excess among men, as compared to the State of California as a whole. Further refinement of this finding showed that it is limited to foreign-born women. The excess is further limited to foreign-born women of Mexican origin, and the excess risk of cancer is approximately threefold within this segment of the population."

These authors think that "this suggests some exogenous factor (or lack of it) peculiar to Mexican-born women and possibly having its major effect prior to emigration."

During the five years 1949-53 a total of 351 residents of California of Spanish surname died of lung cancer, 249 men and 102 women, including 192 foreign-born men and 87 foreign-born women. The mortality for men with Spanish surnames is quite comparable to that for the general male population of California, but the female deathrate is so high that the proportion of women: men is 1:2, while in the general population it is 1:4.8.

The puzzling figures led us to undertake a study of lung cancer in Mexico, using all data available.

The present population of Mexico is slightly over 30 million. As a basis for our study we decided to take the 1940 census figures published by the Mexican Census Bureau, because the young adults of 1940 are by this time mature and it is this group that particularly concerns us. It is mainly the younger age groups that have contributed to the population increase since 1940. Immigration has been rather limited for the last 15 years; European immigration was most copious just after the first and second World Wars.

The Racial Factor

The racial factor is the first to be considered. According to the 1940 census the total population of Mexico in that year was 19,653,552 or about 20 million. The number of Indians of pure lineage is difficult to estimate. The number of persons speaking native Indian languages may give an indirect clue. In 1940 1,486,707 persons over five years of age spoke only one or more native Indian languages or dialects and an additional 1,458,368 spoke both Indian and Spanish.[8] It may be assumed that these groups consist largely of full-blooded Indians. Besides, a number of Indians may, because of their schooling and their contact with mestizos and whites, have learned to speak only Spanish. By a rough estimate we may consider one-third of the Mexican population in 1940 to have been full-blooded Indian; say about 6,000,000.

Mestizos were in the majority; they accounted for about 12 million. Mexican-born whites (creoles) and immigrants from Europe and the United States numbered about 3 million.

Mexican mortality statistics are based on death-certificates of doubtful diagnostic accuracy. Inclusion of metastatic tumors among primary ones of the lung is a source of inaccuracy perhaps even more common in Mexico than elsewhere. In order to study autopsy incidence we had to take recourse to the records of the largest hospitals in Mexico City as samples of the national mortality; however, up to the year 1952 even these were not satisfactorily compiled. Therefore we considered only more recent data.

During the four years 1954-1957, 1,753 autopsies were performed at the General Hospital of Mexico City[9] or 37.09 per cent of all deaths. Of these autopsies, respiratory disease caused death in 984 or 56.14 per cent. Thirty-six primary carcinomas of the lung were found, only one with coexisting tuberculosis. They were grouped as follows:

TABLE I

	Men	Women		Men	Women
Epidermoid	6	4	Kreyberg Group I	21	13
Undifferentiated	15	9	Kreyberg Group II	0	2
Cilindroma	0	1		—	—
Adenocarcinoma	0	1		21	15
	21	15			

Ratio 1.4:1

Comparing these figures with those given by Carl V. Weller[10] for the last 2,000 of a series of 14,000 autopsies performed at the University of Michigan from 1895 to 1954 we find:

TABLE II

	Autopsies	Lung-cancer	Men	Women	Ratio Men:Women
Mexico	1,753	36	21	15	1.4 :1
Michigan	2,000	70	68	8	7.62:1

That is to say: In Michigan distribution of lung-cancer among men is 5.4 times greater than in Mexico. These figures confirm the tendency found by Buechley *et al.*, to a more nearly equal distribution of lung-cancer among Mexican males and females. We interpret these figures to denote a lower incidence of pulmonary cancer among the Mexican population as a whole.

Weller states that in the United States 30 years ago three men suffered from lung-cancer to one woman; Dorn[10] in 1953 found the ratio to be 5:1 (Obviously the increase in lung-cancer has affected principally men).

Farber in 1954[11] found the ratio in 1,070 cases of cancer of the lung, from 19 hospitals in California to be 10 men to 1 woman. Steele in 1954 cited by Weller[10] found in 201 cases:

TABLE III

	Men Per Cent	Women Per Cent
Squamous cell carcinoma	97	3
Undifferentiated	88	12
Adenocarcinoma	65	35

We shall go into these findings in more detail later.

The material that we have selected as a basis for this communication consists of:

1) 9,789 records of private office patients who consulted us for respiratory complaints.
2) Data from the General Hospital of Mexico City and other institutions covering the last 10 years.
3) Other pertinent data.

Clinical Material From Private Practice

From 9,789 histories gathered during 21 years of private office practice 4,129 were selected as being of persons of 35 or more years of age, with 20 or more years' residence in Mexico.

This selection was decided upon because this age-group seemed more suitable for comparison with other authors' work and because in the whole series only three primary cancers of the lung occurred in persons under 35 years of age. All these three cancers occurred in Mexican-born patients.

These 4,129 patients may be grouped by nationality and sex as follows:

TABLE IV

			Per Cent
Mexican-born men	1,690		54
Mexican-born women	1,414		46
Total		3,104	
Foreign-born men	708		69
Foreign-born women	317		31
Total		1,025	
Grand Total		4,129	

Diagnoses of cancer among these patients were grouped as: a) Suspect; b) Characteristic and c) Confirmed.

a) Suspect: Patients whose history, age and relevant symptoms suggested cancer of the lung, but whose study could not be completed.

b) Characteristic: Patients who besides a relevant history had clear-cut roentgenographic evidence of lung tumor, although histological proof could not be obtained.

c) Diagnoses histologically confirmed by smears, biopsy, resection specimens or autopsy.

TABLE V—CASES OF PRIMARY BRONCHOGENIC CARCINOMA FOUND AMONG A TOTAL OF 4,129 PATIENTS WITH RESPIRATORY AILMENTS

A.			Confirmed			106
			Characteristic			42
						148
B. *Mexican-born:*	Men		Women		Total	Ratio Men/Women
Epidermoid	21		6		17	3.66:1
Adenocarcinoma	5		8		13	1 :1.6
Undifferentiated	8		1		9	8 :1
Anaplastic	3		2		5	1.5 :1
Alveolar	1		0		1	
Columnar	1		0		1	
Total		39		17	56	2.3 :1
Unspecified		10		4	14	
Characteristic		19		9	28	
		68		30	98	
C. *Foreign-born:*						
Spaniards:						
Epidermoid	9		1		10	9 :1
Adenocarcinoma	0		0		0	
Anaplastic	1		3		4	
Alveolar	1		0		1	
Unspecified	4		0		4	
Characteristic	5		0		5	
		20		4	24	
Jews:						
Epidermoid	2		1		3	
Adenocarcinoma	1		2		3	
Unspecified	2		0		2	
Characteristic	3		0		3	
		8		3	11	
Other foreign-born:						
Epidermoid	4		0		4	
Adenocarcinoma	2		2		4	
Undifferentiated	1		0		1	
Anaplastic	0		1		1	
Sarcoma	0		1		1	
Characteristic	4		0		4	
		11		4	15	
		39		11	50	3.5 :1

Frequency of Pulmonary Cancer in This Group

	Total	Per Cent	Men	Per Cent	Women	Per Cent	Ratio Men/Women
Foreign-born	50	4.7	39	5.5	11	3.5	1.54:1
Mexican-born	98	3.1	68	4.2	30	2.1	2 :1
Total	148	3.5	107	4	41	2.3	1.7 :1

Group a) Suspect was excluded from this study for obvious reasons.

Compilation of the records of office practice (4,129 patients) and result in figures are given in Table V.

Let me emphasize that neither from these figures nor from others that I present do I pretend to draw conclusions regarding incidence of pulmonary cancer in the general population. I merely wish to call attention to the distribution between the two sexes and to the proportions of the various cytological types. I infer a low incidence of lung-cancer in Mexico from its low preponderance in males, an indirect calculation which serves to strengthen my thesis that the disease is rare in this country.

The word "frequency" is used in this paper to denote the cancer rate in a definite group regardless of time interval; the word "incidence" to denote the yearly rate in the total population.

From these figures we deduce that 3,104 Mexican adults over 35 years of age, sufferers from respiratory disease had a cancer frequency of $\frac{3,104}{98}$ or 1:31.6, while $\underline{1,025}$ foreign-born with more than 20 years' residence in Mexico had a frequency of $\frac{1025}{49}$ or 1:21; that is to say that, in Mexico, among adult sufferers from respiratory complaints, lung cancer occurs $\frac{31.6}{25.0}$ or 1.24 times more frequently in immigrants than in the Mexican-born.

Under the assumption that the Spanish Hospital of Mexico should concentrate an important number of cases of cancer of the lung among Spaniards we asked Dr. A. Izaguirre[30] to compile for us the number of cases observed at the institution and he kindly gave the following data:

From 1947 to 1958 (June), 44 cases of primary cancer of the lung were admitted to that Hospital, mostly Spaniards and all White. (there is no racial discrimination for admission at any hospital of Mexico).

2. Among these 44 cases, 42 were men and 2 women.

3. Among these 42 confirmed cases 38 were smokers (men); none of the women smoked.

4. The age among patients ranged from 43 to 77 years, predominantly from 55 to 70 years. It is pertinent to state that according to the Census (1940) the Spaniards in Mexico City were at that year only 13,855 (0.80 per cent of the population).

Distribution of Pulmonary Carcinoma Between the Two Sexes

Extremely important in every study of endemiology of cancer of the lung is its distribution between the two sexes, not only its distribution in general, but in particular of two groups of cancer, which, according to Kreyberg constitute two separate disease entities. The first group, consisting of epidermoid, anaplastic and undifferentiated growths, predominates in men; the second group, consisting of adenocarcinoma, alveolar cancer and cilindroma, predominates in women. While frequency of the first group varies greatly in different regions of the globe, the second maintains a steady level all over the world. This fact enables us, even in the absence of reliable statistics, to draw some general conclusions, for,

if the incidence of female cancer remains constant, then an increase in the proportion of male cancer would indicate a higher incidence of pulmonary cancer as a whole.

Comparison of our Tables IV and V, B yields an incidence of cancer in the Mexican-born of: Men, 68:1,690 or 1:24.8 and women, 30:1,414 or 1:47.1, that is to say, about two men to one woman with cancer. This low proportion might indicate a low incidence of lung cancer among native-born Mexicans. Comparison of Table IV and V, C yields a frequency of cancer in immigrants of: Men, 38:708 or 1:18 and women, 11:317 or 1:28.8 or a proportion of 1.54 men to one woman with lung cancer.

The findings of Steiner and Buechley *et al.* among Mexican immigrants in Los Angeles are exceptional. It is important to study the varying sex distribution of pulmonary cancer and to make comparisons between different countries.

Campos Rey de Castro[12] and his co-workers grouped Peruvian cases according to Kreyberg's classification. We present the figures of various authors compiled by Campos Rey de Castro *et al.* in the following Table, adding our own for comparison.

TABLE VI

	Kreyberg Type I		Kreyberg Type II	
	Men	Women	Men	Women
Christiansen (Norway)	4.3	1.0	1.2	1.0
Jakobsen (Norway)	6.0	1.0	1.2	1.0
Kreyberg (Norway)	20.0	1.0	1.0	1.0
Ochsner *et al.* (U.S.A.)	11.6	1.0	2.0	1.0
Foot (U.S.A.)	13.0	1.0	1.0	1.0
Ehler *et al.* (U.S.A.)	22.0	1.0	2.7	1.0
Campos *et al.* (Perú)	9.2	1.0	1.1	1.0
Alarcón (México)	3.2	1.0	0.9	1.0

This distribution of all of our cases between the sexes, without reference to cell-type is, in comparison to Buechley's:

TABLE VII

	Men	Women
Alarcón (México) all confirmed cases	2.3	1.0
Buechley (Los Angeles, general population)	4.8	1.0
Buechley (Los Angeles, Mexican-born immigrants)	2.0	1.0

Although these figures may indicate that lung cancer is increasing among Mexican-born women, residents of Los Angeles as well as among Mexican women still living in Mexico, since the figures tend to show a low preponderance of cancerous men over women, they may also indicate that in Mexico men are not developing cancer in the same proportion as women; i.e. that female cancer (adenocarcinoma) keeps the same level in Mexico as elsewhere, but that male cancer (epidermoid) is much less frequent in Mexico than in the United States or Europe.

Frequency of Cancer of the Lung Among Mexicans and Immigrants

We must emphasize that the frequency of cancer of the lung in our patients does not represent its incidence in the population of Mexico as a whole. Ours are not random samples, but are figures taken from patients with respiratory disease. However, even these suggest differences in the racial distribution of pulmonary cancer.

We may point out that the 50 cases of pulmonary cancer that we saw among immigrants occurred in a highly selected sample forming part of a total immigrant population that in Mexico scarcely exceeds 100,000. The 1940 census gives the total number of foreign-born in Mexico as 101,399.[8] The Mexican-born patients, however, come from a rapidly increasing population (20 million in 1940 and 30 million in 1950).

TABLE VIII—PHOTOFLUOROGRAPHY
PREVALENCE OF PRIMARY CARCINOMA OF THE LUNG
IN THE UNITED STATES
Per 100,000

Boucot and Sokoloff[14]			
			Suggestive/Confirmed
For men over 45			556
Guiss Report Los Angeles Survey 1950 (1,867,201 persons X-rayed)			190
A. *Philadelphia 1952:*			
	Confirmed		Rate per 100,000
Total persons under 45 years	4		3
Total persons over 45 years	48		175
Males White over 45 years	27		224
Males non-White over 45 years	20		444
Female White over 45 years	1		13
Female non-White over 45 years			
Over-all Total on 142,156 persons	52		37
Mexico: Per 100,000	Suggestive	Probable	Confirmed
Survey 25,996 persons, Acapulco-Mexico	10	3	
Survey federal employees over 21 years of age (24,717 persons) Mexico City	19		5
			Male: 4 Fem.: 1
1954 Republic of Mexico (Statistics from death-certificates, 493 Ca. Br. per 28,853,428 inhabitants).			
B. *Deaths from lung cancer (certified)*			
1952: Mexico 432	U.S.A. 21,582		
1954: Mexico 493	U.S.A. 25,000 (estimated by E. C. Hammond and Machle)[15]		
C. *Trend of Mortality from Cancer of the Lung in Mexico*			
		Rate Per	
1945	202	0.90 : 100,000	
1946	212	0.93 : 100,000	
1947	261	1.1 : 100,000	
1948	317	1.3 : 100,000	
1949	351	1.4 : 100,000	
1950	346	1.3 : 100,000	
1951	372	1.4 : 100,000	
1952	432	1.5 : 100,000	
1953	445	1.5 : 100,000	
1954	493	1.7 : 100,000	

It is astonishing that we saw so few cancers among Mexican-born nationals who consulted us for respiratory ailments.

Were the Mexican incidence that of the United States one should expect about 4,000 deaths per year from cancer of the lung in Mexico, yet, according to the Census we have only about one-eighth of that number. It is unlikely that the far greater part of Mexican patients with lung cancer die undiagnosed; indeed, it is more likely that most of them with serious respiratory disease sooner or later consult physicians well aware of other ailments besides tuberculosis, for we in Mexico have some 200 chest specialists able to discover or suspect cancer of the lung.

Even if we attempt to correct the incidence derived from the certified deaths, discarding the rural deaths, considering that the urban of Mexico represents only one-third of the whole population, nevertheless the mortality from cancer of the lung remain much lower than that of the United States.

Other Pertinent Data for Comparison Follows

According to Dr. Eduardo García Salazar[15] 3,587 patients were admitted to the Sanatorio Huipulco for treatment of tuberculosis during the last ten years, 2,255 men and 1,342 women. One might assume that a significant number of cancers would be discovered among these supposedly tuberculous patients, but only two were found. This, however, is biased by the fact that patients over 50 years of age are rarely admitted.

In the United States, Alonso de la Fuente at the Sea View Hospital found 34 cases of coexistent tuberculosis and carcinoma in 2,500 autopsies.

Fried, on the other hand found 34 cases of tuberculosis in 319 autopsies where the primary diagnosis was lung cancer.

Pacheco and Rivero[16] inquired among the members of the Mexican Tuberculosis Association regarding the number of cases of cancer in their files. The answers were:

TABLE IX—BRONCHIOGENIC CARCINOMA SEEN BY MEMBERS OF THE MEXICAN TB. ASS'N.

	Number	Per Cent	Ratio Men/Women
Men	888	79.5	3.9:1
Women	228	20.4	
	1,116	99.9	

Figures given by the Department of Pneumonology of the General Hospital in Mexico City are almost identical:

	Number	Per Cent	Ratio Men/Women
Men	144	79.12	3.79:1
Women	38	20.87	
	182	99.99	

Cancer and Tobacco

There are facts demonstrating the relationship between tobacco smoking and cancer of the lung. The long controversy on the subject centers not about the facts but about their interpretation.

Hammond,[17-29] Graham, Wydner,[18] Ochsner[19] and others have given conclusive evidence of "association between cigarette smoking and a few diseases, such as cancer of the lung, cancer of the larynx, cancer of the

esophagus and gastric ulcers, besides other diseases (Hammond).

In Perú Campos Rey de Castro *et al.*[12] also found close association between cancer of the lung and tobacco-consumption.

Increasing frequency of cancer of the lung has been attributed to increasing tobacco-consumption; in Mexico the consumption increased from 33,629 tons in 1945 to 50,991 tons in 1955 (Pacheco).

Conclusions about individual consumption are difficult to reach, because the habit is not equally prevalent among various groups of the population.

We classified the 4,129 cases of respiratory ailments, seen at our office according to their nationality and smoking habits, considering as smokers persons who had smoked ten or more cigarettes per day for twenty or more years. They averaged about twenty cigarettes per day. (141 excluded).

Among our patients, immigrants smoked more than Mexicans; cancer was also more frequent among immigrants than among Mexicans.

Among the men suffering from cancer of the lung in our group, 82 per cent were moderate or heavy smokers and 18 per cent non-smokers.

Some Questions, Largely Unanswered: Any Hypothesis

Why do adult immigrants from the United Kingdom to New Zealand, from Europe to Israel and from Europe to Mexico have a higher lung cancer-rate than natives of these countries?

TABLE X—SMOKING HABIT AMONG 3,988 PERSONS SUFFERING RESPIRATORY AILMENTS

	Total		Nonsmokers		Smokers		Ratio Nonsmokers/ Smokers
Mexicans, all races predominantly mestizo:							
Men	1,690		1,400		290		4.8:1
Women	1,414		1,342		72		18.7:1
		3,104		2,742		362	
Immigrants over 35 years Mexico-resident over 20 years:							
a) *Spaniards:*							
Men	156		87		69		1.3:1
Women	28		27		1		27.1:1
		184		114		70	
b) *Jews:*							
Men	240		150		90		1.7:1
Women	175		148		27		3.5:1
		415		298		117	
c) *Near Orientals:*							
Men	150		105		45		2.3:1
Women	65		60		5		12 :1
		215		165		50	
d) *U.S.A.:*							
Men	19		12		7		1.7:1
Women	9		6		3		2 :1
		28		18		10	
e) *Canton-China:*							
Men	42		40		2		20 :1

Why do Mexican-born women who settle in Los Angeles develop epidermoid cancer more frequently than American-born Mexican and white women living in the same city?

Paul E. Steiner[24] found in the Los Angeles Study in the Mexican group some interesting characteristics.

Among 6,150 autopsies 590 malignant tumors were found. Although cancers were present in smaller proportion in all autopsies of Mexicans than in those of Caucasoids the distribution of the carcinomas was peculiar: Mexicans have relatively fewer carcinomas of the large intestine, prostate, breast, esophagus (males), urinary bladder (males), and ovary and of the lymphatic diseases and intracraneal tumors. On the other hand they had significantly more chorionepitheliomas and carcinomas of the lung, larynx and gall bladder, all in women, and of bone tumors in men. The other tumors were not significantly different.[24]

Data here presented lead us to believe that race and heredity do not determine this difference; New Zealand immigrants and native-born New Zealanders are of the same stock.

In Mexico: (1) Cancer of the lung is more frequent among white immigrants than among native mestizos. It is extremely rare among full-blooded Indians; of our 148 cancer patients only three were Indians. It well may be that striking differences or habits, food and exposure are more important than race.

This finding is in accord with the numbers published by Campos Rey de Castro from the National Institute of Cancer of Peru.[12]

This author presents the following among 175 cases studied from 1952 to 1957:

	Number	Per Cent	Per cent of population
Mestizos	68 cases	(57.6)	52.9
Whites	38 cases	(32.2)	
Mongolians	11 cases	(9.3)	0.7
Indians	1 case	(0.8)	45.8
Negroes	0 cases	(0.0)	0.5

The food containing fats and rich in cholesterol have become suspect of being carcinogenic since the experiences of Shabad (1937), Hieger (1940), Steiner (1941) and Guerin (1941)[28] Hieger concludes that "the carcinogenic activity of cholesterol has been demonstrated. Seventy sarcomata were induced in 1,414 mice (initially) by the injection of oily solutions of cholesterol. The incidence is variable; it fluctuates between about 14 per cent and zero."

In this connection is pertinent to present the consumption of fats in Mexico and the United States and other countries as these differences may count as relative factors.

(2) Primary cancer of the lung is increasing in Mexico, but it still is much rarer than it is in the United States or Europe.

(3) The more reliable Mexican statistics give a sex-distribution ratio for cancer of the lung from 3.9 to 2 men to 1 woman. This is comparable to the ratio 4.8:1 found among the Los Angeles general population, but differs slightly from the 2:1 ratio found by Buechley *et al.* for Mexican-born residents of Los Angeles. The ratio of our combined material is 2.6 men to 1 woman.

(4) Smoking is a habit more frequent among immigrants from Europe to Israel,[4] to New Zealand[2] and to Mexico, as our statistics show. We find a relation between the smoking habits of various racial groups in Mexico and their cancer-incidence. Indians rarely smoke; Mexican mestizos smoke only one-third as often as Spanish and Jewish immigrants (see Table X).

(5) Diet: The food of full-blooded Mexican Indians and Mexicans predominantly Indian by racial characteristics, color and habits is greatly deficient in animal proteins and poor in fat. Pulmonary cancer and vascular disease (atheroma and sclerosis) run parallel. Cholesterol is probably a carcinogenic substance, contained mainly in food.

(6) Cancer in women: In Mexico few mestizas (feminine) smoke; their diet is poor in meat, butter and saturated fats. When they settle in the United States they readily begin to smoke and adopt the diet of a country rich in these foods.

O. Mittman from Bonn[22] studied the correlation between consumption of meat and incidence of cancer in several countries although he did not mention the countries included.

From the statistical and mathematical study he concluded that there is definite correlation between consumption of certain animal food and cancer, and on the contrary, meat from certain animals is not carcinogen and even may play a role in prevention.

The meats and other animal foods which he considers cancerigenous are: pork, milk derivatives, animal fats and oils.

On the other hand he claims that from his studies meat from lamb, goat, fowl, horse and wild animals are anti-cancerous.

TABLE XI—FATS AND OILS CONSUMPTION IN SEVERAL COUNTRIES (22)

Country	Year	Edible fats and oils Kg. per capita
India	1957	4.5
Argentine	1956	16.8
Brazil	1955	8.2
France	1957	20.0
Italy	1957	14.0
Spain	1957	14.5
Great Britain	1957	21.0
United States	1956	30.3
México	1957	7.5 (21)

Some other factor peculiar to Los Angeles immigrants must account for the frequency of lung cancer among women immigrants; as in San Francisco they are not thus affected. Perhaps smog and the fumes of countless automobiles may play a role. There may be still other factors.

Mexican women living under similar conditions, but born in the United States do not react in the same way to their environment.

A vital infection, incurred prior to emigration, latent, like many viral infections, for long periods of time until a sudden provocation arouses the neoplasm to activity—such an hypothesis may explain the difference; or else, exposure to foreign viruses to which no previous immunity exists, which, added to carcinogenous irritants, awaken neoplastic activity.

The assumption that a combined action of several carcinogens is necessary for the development of cancer of the lung is also sustained by the Duran Reynals experiments showing as this author states "that neoplasia by chemicals and hormones is mediated by viruses and . . . that, in some cases at least these viruses may be of the ordinary, inflammatory and necrotizing type which under certain circumstances, may change into or function as neoplastic viruses" (Duran Reynals-Studies).[23]

To this attractive hypothesis the new knowledge of the experimental concepts of latency, inhibition and masking of viruses as expounded by Huebner,[25] Andervont,[26] Goodpasture[27] in 1957 give support to the possibility of a dormant viral infection as a factor for the development of cancer of the lung.

This hypothesis is the only offering an explanation for the described phenomenon of the paradoxically high, incidence of cancer of the lung among Mexican women in Los Angeles.

This pathogenic concept has been applied to cancer in other organs. It may explain variations in geographical incidence of cancer and the difference between natives and immigrants.

SUMMARY

This study is based upon 4,129 patients who consulted the author for respiratory disease. All these patients were over 35 years of age.

From frequency of cancer of the lung among patients seen in our office, among patients of the General Hospital of Mexico City and from data of other surveys of different groups we infer that this disease is rare in Mexico compared with other countries. In Mexico lung cancer tends to be equally distributed between men and women. This is interpreted as indicating that the epidermoid type is less frequent among men, while adenocarcinoma maintains a constant rate among women. However Mexican women have a slightly higher proportion of epidermoid cancer than might be expected.

In Mexico cancer of the lung is more prevalent among Whites who immigrated after they were 35 years of age and who have resided in the country for over 20 years than among native-born Mexicans.

Among the author's patients complaining of respiratory ailments, lung cancer was found 50 per 1000 persons in immigrants over 35 years of age who had lived in Mexico over 20 years; the frequency in a comparable group of native-born Mexicans over 35 years of age is 32:1000.

Full-blooded Indians rarely suffer from lung cancer; of our 148 cancer patients only three were Indians.

The ratio of men to women who suffered from lung cancer was: for immigrants, 3.5:1.0; for native Mexicans 2.3:1.0.

The relatively low ratio may have to do with the infrequency of pulmonary cancer in Mexico. The female incidence remains about the same all over the world; the male incidence varies. To this general rule, the frequency of cancer among Mexican women immigrants to Los Angeles forms an exception.

The ratio of smokers to nonsmokers in the immigrant group is: for male Spaniards, 1:1.3; for male Jews, 1:1.7. The ratio for Mexican-born males is 1:4.8. The ratio for all women is 1.0:14.8, for Jewish women, 1:5.5.

Lung cancer is more frequent among adult immigrants to New Zealand, Israel, Mexico and the City of Los Angeles than among native residents of these places.

Lung cancer is much less frequent in Mexico than in the United States or in Europe, according to our estimate, about eight times less frequent. Nevertheless, Mexican incidence is increasing. Certified deaths in 1945 numbered 0.90 per 100,000 and in 1954, 1.7 per 100,000.

Causes of variations in incidence may lie in varying amounts of carcinogens contained in the air and in food; a virus of multiple viruses may be another adjuvant factor.

Until a determining factor is found, prevention of cancer of the lung must lie in control and avoidance of known carcinogenic factors.

RESUMEN

Este estudio está basado en la revisión de las historias clínicas de 4,129 enfermos que consultaron al autor con motivo de padecimientos respiratorios.

De acuerdo con la frecuencia con que se ha visto el cáncer pulmonar en este grupo así como lo que se pudo conocer que ocurrió en el Hospital General y en otros establecimientos de México, inferimos que esta enfermedad es relativamente rara o poco frecuente aún, al compararse con lo que sucede en otros países. En México el cáncer pulmonar tiende a distribuirse igualmente entre hombres y mujeres. Esto lo interpretamos como que el tipo epidermoide es menos frecuente entre los del sexo masculino, en tanto que el adenocarcinoma y formas histológicamente asimilables mantiene una proporción constante entre las mujeres. Sin embargo, las mujeres mexicanas muestran una ligera proporción mayor de cáncer epidermoide que lo esperado. En México el cáncer del pulmón es más prevalesciente entre los de raza blanca que inmigraron después de los 35 años de edad y que han residido en el País por 20 o más años en comparación con la frecuencia entre los mexicanos de nacimiento de edad semejante.

Entre los pacientes vistos por el autor, por quejarse de padecimientos respiratorios, el cáncer se encontró aproximadamente en proporción de 50 por cada 1,000 inmigrantes en las condiciones antes señaladas de más de 35 años y que han vivido más de 20 años en México; la frecuencia en un grupo comparable de mexicanos de nacimiento mayores de 35 años, es de 32 casos de cáncer pulmonar por 1,000 enfermos respiratorios. Los indios de raza pura, rara vez enferman de cáncer pulmonar; entre los 143 casos observados sólo se encontraron tres indios puros.

La relación de hombres/mujeres que sufrieron cáncer del pulmón en este grupo estudiado, fué para los inmigrantes 3.5:1; para los nacidos en México (todas las razas) fué de 3.2:1.

Es de notarse que en grupos muy selectos de inmigrantes españoles se ha obtenido una relación de hombres a mujeres de 1:21, si bien la inmigración de mujeres es mucho menor que la de hombres.

La proporción de cáncer entre ambos sexos, relativamente baja puede ser debida en general a la infrecuencia del cáncer en México. La incidencia del cáncer pulmonar femenino es aproximadamente la misma en todo el mundo, es el cáncer pulmonar en el sexo masculino el que varía. A esta regla general hace excepción la frecuencia del cáncer pulmonar entre las mujeres mexicanas que han emigrado a Los Angeles, California.

La relación de fumadores a no fumadores en el grupo total de inmigrantes es para los españoles hombres de: 1:1.3; para los judíos hombres: 1:1.7. Para los mexicanos de nacimiento es: 1:4.8. La relación de fumadoras y no fumadoras (todas mujeres) es 1:14.8 y para las mujeres judías es 1:5.5.

En el grupo total de enfermos de cáncer pulmonar, 82% eran fumadores moderados y grandes fumadores y 18 por ciento no eran fumadores.

El cáncer del pulmón es más frecuente en los adultos inmigrantes a Nueva Zelandia, Israel, México y la Ciudad de Los Angeles que entre los nativos de esos países y ciudades.

El cáncer del pulmón en general, es mucho menos frecuente en México que en los Estados Unidos o en Europa. De acuerdo con nuestra estimación es ocho veces menos frecuente.

Sin embargo, el cáncer del pulmón está aumentando en México. Las muertes certificadas en 1945 por cáncer del pulmón, fueron de 0.90 por 100,000 en 1945 y en 1954 fueron 1.7 por 100,000 habitantes.

Las causas y las variaciones de la incidencia, pueden radicar en las diferentes cantidades de carcinógenos contenidos en el aire y en los alimentos; un virus o virus múltiples puede ser otro factor aún poco investigado.

Mientras no se encuentre el factor principal determinante, la prevención del cáncer pulmonar debe basarse en el control y la supresión de los factores carcinogénicos conocidos.

RESUME

Cette étude est basée sur 4.129 malades qui consultèrent l'auteur pour affection respiratoire. Tous ces malades avaient dépassé l'âge de 35 ans.

D'après la fréquence du cancer pulmonaire parmi les malades vus dans sa consultation, parmi les malades de l'Hôpital Général de Mexico et d'après les constatations des autres contrôles faits dans différents groupes, l'auteur infère que cette affection est rare à Mexico, comparativement aux autres pays. A Mexico, le cancer pulmonaire semble être également réparti entre hommes et femmes. Ceci est interprété comme une indication selon laquelle le type épidermoïde est moins fréquent chez les hommes, tandis que l'adéno-carcinome se maintient à un taux normal chez les femmes. Cependant, les femmes Mexicaines ont une proportion légèrement supérieure de cancer éipdermoïde qu'on ne pourrait l'attendre.

A Mexico, le cancer du poumon est plus fréquent chez les Blancs qui ont immigré après avoir atteint 35 ans et qui ont résidé dans la campagne pendant plus de 20 ans que chez les Mexicains nés dans le pays.

Parmi les malades de l'auteur se plaignant de troubles respiratoires, le cancer pulmonaire fut découvert chez 50 personnes sur 1.000 chez les immigrants de plus de 35 ans qui avaient vécu à Mexico pendant plus de 20 ans; la fréquence du cancer, dans un groupe comparable de Mexicains nés dans le pays et ayant dèpassé 35 ans est de 32 pour 1.000.

Les Indiens de race pure sont rarement atteints de cancer pulmonaire; sur 148 malades cancéreux, trois seulement étaient Indiens.

La proportion d'hommes et de femmes atteints de cancer pulmonaire fut: pour les immigrants de 3,5 à I; pour les Mexicains natifs de 2,3 sur I.

Le rapport relativement faible peut être lié à la rareté du cancer pulmonaire à Mexico. Le taux des atteintes féminines reste environ le même partout dans le monde; le taux masculin varie. La fréquence du cancer parmi les femmes Mexicaines immigrées à Los Angeles constitue une exception à cette règle générale.

Le rapport des fumeurs aux non-fumeurs dans le groupe des immigrés est: pour les hommes d'origine espagnole I sur 1,3; pour les hommes d'origine juive: 1 à 1,7. Le rapport pour les hommes nés au Mexique est de 1 à 4,8. Le rapport pour toutes les femmes est de 1 á 14,8 et pour les femmes juives de 1 à 5,5.

Le cancer pulmonaile est plus fréquent chez les immigrés en Nouvelle Zélande, en Israêl, au Mexique et dans la ville de Los Angeles que parmi les résidents natifs de ces endroits.

Le cancer pulmonaire est beaucoup moins fréquent au Mexique qu'aux Etats-Unis ou en Europe, environ 8 fois moins fréquent selon l'estimation de l'auteur.

Néanmoins, cette fréquence Mexicaine est en train d'augmenter. Les décès certifiés par cancer donnaient 0,90 pour 100.000 en 1946, 11,7 pour 100.000 en 1954.

Les causes de variations de fréquence peuvent rèsider dans les différentes quantités de carcinogènes contenus dans l'air et la nourriture; un virus ou de multiples virus peuvent être un autre facteur adjuvant.

Jusqu'à ce que le facteur déterminant ait été trouvé, la prophylaxie du cancer pulmonaire doit consister à contrôler et à éviter les facteurs carcinogènes connus.

ZUSAMMENFASSUNGEN

Diese Untersuchung basiert auf 4 129 Patienten, die den Verfasser konsultierten wegen Erkrankungen der Atmungsorgane. Alle diese Kranken waren mehr als 35 Jahre alt.

Wir schliessen aus der Frequenz von Lungenkrebsfällen bei Patienten, die wir in unserer Praxis sahen, bei Patienten des Allgemeinen Krankenhauses der Stadt Mexiko, sowie aus Daten von anderen Untersuchungen an verschiedenen Bevölkerungsgruppen, dass diese Krankheit in Mexiko selten ist im Vergleich zu anderen Ländern. In Mexiko neigt der Lungenkrebs zu einer gleichmässigen Verteilung zwischen Männern und Frauen. Dies wird interpretiert als Indikator dafür, dass der epidermoidale Typ bei Männern weniger häufig vorkommt, während das Adenocarzinom sich in konstanter Rate bei Frauen behauptet. Es weisen jedoch die mexikanischen Frauen einen etwas höheren Satz an Epidermoid-Krebsfällen auf, als man erwarten würde.

In Mexiko kommt der Lungenkrebs häufiger unter denjenigen Weissen vor, die bei der Einwanderung mehr ais 35 Jahre alt waren und die mehr als 20 Jahre im Lande wohnten als unter den eingeborenen Mexikanern.

Unter den Kranken des Verfassers, die über respiratorische Erkrankungen klagten, fand sich der Lungenkrebs bei 50 auf 1000 Personen unter den Einwanderen über 35 Jahre, die in Mexiko mehr als 20 Jahre gelebt hatten; die Frequenz in einer vergleichbaren Gruppe von eingeborenen Mexikanern im Alter über 35 Jahre beträgt 32: 1000.

Vollblutindianer erkranken selten an Lungenkrebs; unter unseren 148 Krebskranken waren nur 3 Indianer.

Das Verhältnis von Männern zu Frauen, die an Lungenkrebs litten, betrug für Einwanderer 3,5: 1,0; für eingeborene Mexikaner 2,? : 1,0.

Die relativ niedrige Verhältniszahl hängt vielleicht zusammen mit der geringen Häufigkeit von Lungenkrebsfällen in Mexiko. Die Häufigkeit beim weiblichen Geschlecht bleibt ungefähr die gleiche in der ganzen Welt; die Häufigkeit bei Männern wechselt. Gegenüber dieser allgemeinen Regel bildet die Häufigkeit des Krebses bei die nach Los Angeles eingewanderten Mexikanerinen eine Ausnahme.

Das Verhältnis von Rauchern zu Nichtrauchern in der Gruppe der Einwanderer lautet: für Spanier männlichen Geschlechts 1: 1,3; für Juden männlichen Geschlects 1: 1,7; Das Verhältnis für eingeborene mexikanische Männer lautet 1: 4,8. Das Verhältnis für alle Frauen beträgt 1,0: 14,8, für Jüdinnen 1: 5,5.

Der Lungenkrebs ist häufiger bei männlichen Einwandern aus Neuseeland, Israel, Mexiko und der Stadt Los Angeles als bei den dort Aufgewachsenen.

Der Lungenkrebs ist in Mexiko weit weniger häufig als in den Vereinigten Staaten oder in Europa, und zwar nach unserer Schätzung ungefähr 8 mal weniger.

Trotzdem nimmt aber die Häufigkeit in Mexiko zu. Die bestätigten Todesfälle betrugen 1945 0,9 auf 100 000 und 1954 1,7 auf 100 000.

Die Ursache für diese verändere Häufigkeit kann in verschieden starken carzinogenen Substanzen liegen, die in der Luft und in der Nahrung enthalten sind; ein Virus oder mehrere Viren können ein weiterer zusätzlicher Faktor sein. Solange, bis ein determinierender Faktor gefunden worden ist, muss die Krebsverhütung in der Bekämpfung und Vermeidung bekannter carzinogener Faktoren liegen.

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An Outbreak of Asian Influenza in Tuberculous Patients*

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During the latter part of September, 1957, a small outbreak of Asian influenza occurred among a group of tuberculous children who were patients in the Olive View Sanatorium. The outbreak was confined to children on one ward; this limitation of spread was accomplished, in part, because (1) of the strict isolation practices carried on by the staff and personnel at all times, and (2) by the immediate initiation of a vaccination program.

The purpose of this paper is to report a clinical and serological study of the patients involved in the outbreak. There have been no reports in the literature of infection with Asian influenza superimposed on individuals infected with tuberculosis. Our study shows that these individuals are capable of an "immune response" similar to that of a non-tuberculous population and that, in the great majority of patients, influenza did not appear to influence the tuberculosis adversely.

Clinical Observations

WMC, a girl six years of age, was admitted to the Sanatorium on September 24, with a slight fever and history of a cold which was improving. By September 28, three patients on the girls' ward to which WMC was admitted, were running a high temperature. Within two weeks, 29 out of the 31 girls assigned to this ward, had had fever with symptoms of influenza. Also, the ward personnel had fever and generalized malaise with "chest cold" and cough.

In most cases, the clinical course of the disease was uneventful. There was a gradual onset of fever, usually starting at 100.2 and increasing up to 101 to 104° F within four to six hours. Duration of fever was from two to three days. Patients were afebrile by the fifth day. There was marked lethargy during the period of high fever. The complaints were of sore-throat, headache, coryza, and "general aches and pains." Several patients had abdominal pain, nausea, vomiting, and anorexia. Nonproductive cough persisted for several weeks. Physical examination was negative except for pharyngitis. In some cases, the tonsils were enlarged and inflamed. "An utter lack of cheer" characterized the episode.

In efforts to evaluate the effect of a superimposed viral respiratory infection upon an existing tuberculous infection, the patients were followed for several weeks after the influenza had subsided. These studies included physical examinations, x-ray films, and laboratory tests.

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Control Measures

The ward was quarantined from September 30 to October 27, and visitors were not allowed. The patients were confined to bed except for bathroom privileges and did not leave, even for x-ray films or clinics. Those with fever were confined to bed without bathroom privileges.

On October 18, when the serum specimens from the first patients began to show a rise in HI antibody titer against Asian influenza virus, a vaccination program was initiated. Patients in wards immediately adjacent to the ward where the outbreak had occurred were vaccinated within 24 hours along with other patients considered to be at a greater risk. The latter group included diabetics, surgical cases, and children. Within 72 hours, the remainder of the patients along with all the sanatorium personnel had been vaccinated. A commercial monovalent Asian influenza vaccine containing 200 CCA units/ml. was employed; each subject received 0.5 ml. (100 CCA units) by intradermal injection.

Laboratory Methods

Acute and convalescent serum specimens were collected and tested for specific antibody against the Asian strain of influenza virus. Hemagglutinating and soluble complement-fixing antigens were prepared by standard techniques (1) employing the A/Japan/305/57 strain of virus.[2] The sera were titrated both for hemagglutination-inhibiting (HI) antibody and for complement-fixing (CF) antibody. Because infection with one strain of Type A virus will stimulate an increase in the level of preexisting antibody to other Type A strains, with which the patient has had previous experience,[3] the sera were tested for HI antibody to two additional Type A, prototype viruses. The additional lines of virus employed were the PR8, Type A, and FM1, Type A′.

Titrations for HI antibody were performed by standard methods (1) employing human "O" red blood cells. The serum specimens were uniformly treated with potassium periodate (2) in order to destroy nonspecific HI inhibitors which may interfere with the tests. The HI serum titers were recorded as the initial dilution of serum which completely prevented hemagglutination.

Titrations for CF antibody were carried out by standard procedures.[1]

In order to evaluate the efficacy of Asian influenza vaccination in a tuberculous population, 100 patients were selected at random and their sera examined for HI antibody to the vaccine as described above.

Results

Detailed, pertinent data from serum titrations on half the patients involved in the outbreak of Asian influenza are recorded in Table I. The remainder of the data is similar to that recorded and is, therefore, omitted. As can be seen, there has been a significant rise in both HI and CF titers to Asian influenza. An HI titer in the acute phase serum was found in only one patient (Case 1, WMC) and this was the original contact case. Of 31 patients on the ward, only two, Cases 12 (MD) and 13 (NP), did not have "clinical" influenza. Apparently, both of them had a sub-clinical infection as evidenced by a rise in HI and CF antibody. Case

Number 14 (LR) and 15 (EH) had no rise in HI antibody, but exhibited a significant rise in CF antibody; both patients had "clinical" disease. As would be expected in this age group, a concomitant rise in antibody titer to the FMI or A′ strain of virus was demonstrated in the majority of individuals. It is interesting to note that antibody titer to the PR8 strain of virus rose only in patients 11 years of age or older. This rise in antibody titer to related virus strains is probably conditioned by previous antigenic experience and has been described as the "doctrine of original antigenic sin."[3] The antibody titer to the antigen first experienced by an individual may show a greater rise than the titer to the current antigenic stimulus, provided the two are closely related. This set of events results from an anamnestic or recall phenomenon[3] and is clearly shown in the results of this study.

With the exception of Cases 4 and 10, infection with Asian influenza virus had no detectable untoward effect on the status of the patient's tuberculosis. Gastric lavages were cultured for tubercle bacilli (one lavage from each patient) and were uniformly negative. Blood counts and sedimentation rates did not differ markedly from the values obtained previous to the viral attack; the total WBC's ranged from 6,000 to 8,450 with PMN's ranging from 22 to 64 per cent and lymphocytes from 19 to 67 per cent. The sedimentation rates reflected the state of the patient's tuberculosis and were not changed with the exception of Case 10 in which the rate was greatly increased.

X-ray films taken after the infection subsided showed continued improvement of the tuberculosis except in the two cases mentioned above. The x-ray films on Case 4 showed an increase in perihilar nodes with increased infiltration on the right side. Subsequent x-ray films have shown a regression of this initial increase. On Case 10, x-ray films revealed an increased infiltration around a cavity with enlargement of the cavity; subsequent x-ray films have shown a progressive increase in these processes (films of December 11, 1957 and January 27, 1958). It is of interest, also, to note the high CF titer (2048) of the convalescent serum from this patient. Both of these patients had had previous experience with influenza virus as shown by the titers to FM1 virus found in their sera.

The HI antibody responses of 100 tuberculous patients to vaccination with 100 CCA units of Asian influenza vaccine are recorded in Figure 1. The sera were collected six weeks after vaccination. The individuals tested were chosen at random and ranged in age from 15 to 85 years. Because of this random age distribution, the data were recorded to show the relative antibody response with respect to age. It is evident that the greatest responses were among older age groups. HI antibody, measurable at a 1:10 dilution of serum, was not found in 43 of the 100 individuals tested; the average age of this group was 41 years. The group which showed titers of 1:10 comprised 23 individuals who had an average age of 39 years. Twelve individuals showing a titer of 1:20 were, on the average 47 years of age; a total of seven with an average age of 54 showed titers of 1:40; nine with average age of 57 showed titers of 1:80; four with an average age of 58 showed titers of 1:160; and two individuals with an average age of 70 years had titers greater than 1:640. The greater responses seen

in older individuals may represent, in part, an anamnestic response to an antigen with which the subjects had had previous experience. It has been postulated that the antigens of Asian influenza are closely related to antigens of the influenza virus which caused the pandemic of 1889-90.[4] This strain of influenza was apparently prevalent until it was replaced by the antigenically different strain of the 1918-19 pandemic. In this study, only four individuals under 50 years of age showed titers of 1:40 or greater and they were 42, 45, 48, and 48 years old.

Individuals 50 years of age and older could have had previous experience with antigens of virus strains prevalent during the 1888-1918 period. They would be expected to show greater antibody responses to Asian influenza than persons born after this period. Since the strain of virus responsible for the 1898 pandemic was not isolated and studied, these observations remain in the realm of speculation. However, there is serological evidence that the 1889 strain was antigenically similar to that of the Asian strain.[4, 5]

The response of tuberculous patients to influenza vaccination appears to be similar to that of non-tuberculous populations. These results, including the finding that 43 individuals showed no measurable HI antibody at the serum dilution of 1:10, are similar to results obtained by other investigators employing comparable doses of vaccine[6] in a normal group of individuals.

Comments

Strict isolation procedures are carried out at Olive View by the staff and ward personnel; gowns, and masks are used at all times by *everyone*. These practices help to protect the attending personnel against tuberculosis, but are, ordinarily, considered to be of little value in preventing

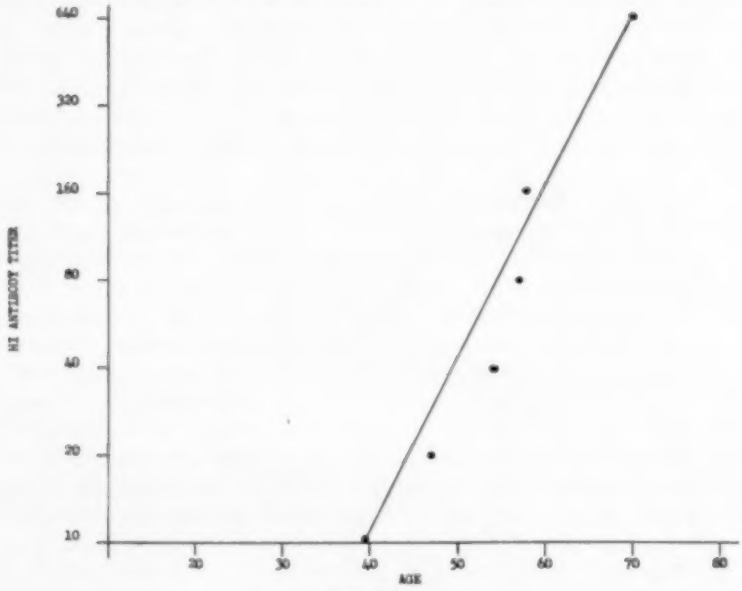

FIGURE 1

the spread of influenza because exposure has usually taken place before diagnosis is made. However, in the situation existing at Olive View, isolation precautions were in operation at all times during the outbreak and undoubtedly helped to limit the spread of influenza.

The prompt vaccination of all sanatorium personnel and all patients, other than those involved in the outbreak, may have been another factor in limiting the spread of the infection. Although the ward attendants in the girls' ward where the outbreak occurred were vaccinated, they developed clinical influenza. Because of their intimate contact with the infected children over extended periods of time, their chances of exposure must have been greatly increased. Exposure probably preceded vaccination. It is probable that the 100 CCA units of monovalent Asian influenza vaccine employed was insufficient to induce optimal immunity. Among the 100 sera tested for HI antibody response to vaccination, titers of 1:10 (the lowest dilutions of serum tested) were not found in the sera from a total of 43 individuals. Although, in these individuals, vaccination was not followed by an antibody response measurable by the test employed, some immunity may have been effected. It has been shown that certain individuals, although they show no detectable antibody response to Asian influenza vaccination, have, nevertheless, a degree of immunity when exposed to infection.[6]

The dependence of HI antibody levels upon age was found to be statistically significant. Log_2 titers of HI antibody were plotted against the ages of the 100 individuals tested and regression lines indicating the effect of age on titer and *vice versa* were determined.* These results

*The statistical analysis was made by Dr. Wilfrid J. Dixon, Professor of Biostatistics, UCLA Medical Center.

TABLE I

THE SEROLOGIC RESPONSE OF A GROUP OF TUBERCULOUS PATIENTS TO ASIAN INFLUENZA

Case Number	Age in Years	Viral Antigens: PR8 HI Titer A*	PR8 HI Titer C**	FM1 HI Titer A	FM1 HI Titer C	Asian HI Titer A	Asian HI Titer C	Asian CF Titer A	Asian CF Titer C
1 (WMC)	6	<10	<10	20	20	20	80	0	16
2 (AR)	6	<10	<10	<10	<10	<10	80	0	32
3 (NA)	5	<10	<10	10	20	<10	40	±	128
4 (MO)	4	<10	<10	10	80	<10	40	0	16
5 (RM)	7	<10	<10	20	80	<10	20	±	256
6 (ROM)	6	<10	<10	20	40	<10	40	4	64
7 (GH)	6	<10	<10	<10	<10	<10	40	0	64
8 (DC)	7	<10	<10	40	40	<10	20	4	128
9 (AG)	12	<10	<10	<10	10	<10	40	0	0
10 (SR)	9	<10	<10	20	80	<10	80	0	2048
11 (GG)	7	<10	<10	<10	20	<10	40	0	128
12 (MD)	14	<10	10	20	40	<10	10	0	32
13 (NP)	14	<10	<10	20	40	<10	20	0	16
14 (LR)	15	<10	10	80	320	<10	<10	0	16
15 (EH)	11	<10	10	20	20	<10	<10	0	32

*Acute serum specimen.
**Convalescent serum specimen.

revealed that a 10-fold increase in antibody titer is associated with each 17 years' increase in age in the 15-85 year age group tested. Conversely, each years' increase in age corresponded to a $\log_2$ titer increase of approximately 0.014 or 3.1 per cent. The probability is less than 0.01 that the effect of age on titer was a chance occurrence.

The significance of the worsening of tuberculosis in patient 10 is difficult to determine. This child was admitted to the sanatorium with tuberculosis. Diagnosis had been made on the basis of x-ray film examination and a positive gastric lavage culture for *M. tuberculosis*. The strain of *M. tuberculosis* was found to be antibiotic-sensitive and the patient was treated with PAS in combination with streptomycin and INH. Her tuberculosis showed satisfactory improvement up to the time of the influenza outbreak. Gastric lavage cultures for *M. tuberculosis* which had become negative have not reverted to positive in spite of the change in disease status.

Ordinarily, patients on the ward where the influenza outbreak occurred, progress satisfactorily. They are ambulatory; their cultures are negative for tubercle bacilli and they can be expected to progress to full recovery. Many of the children placed here, as in the case of the original influenza contact case, are admitted to the sanatorium only because of a tuberculin conversion and/or x-ray film evidence of early tuberculosis and positive cultures are not obtained. Whether or not the attack of influenza affected the tuberculosis of the one patient to a greater degree than it did in the remaining patients is not known. However, on the basis of the recovery which is predicted for almost 100 per cent of the patients on this ward, one may suspect that the viral infection influenced the tuberculosis adversely. This patient's progress will continue to be watched with particular interest.

SUMMARY

An outbreak of Asian influenza which occurred in a tuberculosis sanatorium was limited to a single ward. All of the 31 girls confined to this ward contracted the infection as judged by an increase in titers of both HI and CF antibody against Asian influenza virus. However, in spite of a rise in antibody titer, two of the girls showed no clinical symptoms. The immune response of these tuberculous patients was similar to the immune response seen in non-tuberculous individuals. Also, the HI antibody response to Asian influenza vaccine was comparable to that of normal populations given a similar dosage of vaccine.

Except in two individuals, the viral infection did not appear to affect adversely the tuberculous disease present in these patients. In one of the two cases, the adverse effect was reversed within a period of two months and the patient's tuberculosis has since continued to improve. The tuberculosis of the other patient has continued to worsen since the onset of the viral infection.

RESUMEN

Un brote de influenza asiática que se desarrolló en un sanatorio para tuberculosis se limitó a una sala.

Todas las mujeres confinadas en ese servicio contrajeron la infección a juzgar por el aumento en los títulos de los anticuerpos HI y CF contra el virus de la influenza. A pesar del aumento en la titulación de anticuerpos, dos de las mujeres no tuvieron síntomas. La respuesta inmunitaria de estas tuberculosas fué similar a la respuesta inmunitaria de las personas no tuberculosas. También la respuesta del anticuerpo HI con la vacuna contra la influenza asiática fué comparable a la obtenida en personas normales.

Con excepción de dos personas, la infección viral al parecer no afectó adversamente a la evolución de la tuberculosis en estas enfermas. En uno de los dos casos efectos adversos retrocedieron al cabo de dos meses y desde entonces la enforma ha continuado mejorando. La tuberculosis en la otra enferma ha continuado empeorando desde el principio de la infección viral.

RESUME

Une attaque de grippe asiatique qui survint dans un sanatorium se limita à une seule salle d'hospitalisation. Les 31 jeunes filles confinées dans cette salle contractèrent toutes l'infection si l'on en juge par l'aufmentation des titres des anticorps HI et CF contre le virus de la grippe asiatique. Cependant, malgré une élévation du titre des anticorps, deux des peunes filles ne présentèrent aucun symptôme clinique. La réponse immunologique de ces malades tuberculeuses fut semblable à celle constatée chez des individus non-tuberculeux. La réponse de l'anticorps au vaccin contre la grippe asiatique fut également comparable à celle des populations non malades ayant reçu une dose semblable de vaccin.

Sauf pour deux d'entre elles, l'infection virale ne sembla pas influencer fâcheusement la maladie tuberculeuse dont étaient atteintes ces malades. Dans un de ces deux cas, cette action défavorable fut annulée en deux mois et la tuberculose de la malade a continué depuis à s'améliorer. La tuberculose de l'autre malade a continué á s'aggraver depuis l'apparition de l'infection virale.

ZUSAMMENFASSUNG

Der Ausbruch einer asiatischen Grippe, der sich in einer Tuberkulose-Heilstätte ereignete, wurde auf eine einzige Abteilung begrenzt. Sämtliche 31 auf dieser Abteilung untergebrachten Mädchn zogen sich die Infektion zu, wie sich an einem Anstieg des Titers sowohl für HI wie für CF-Antikörper gegen asiatische Grippe-Virus ergab. Es zeigten jedoch trotz einem Anstieg des Antikörper-Titers zwei der Mädchen keine klinischen Symptome. Die immunbiologische Antwort dieser tuberkulösen Patienten ähnelte der immunbiologischen Antwort, die man bei nicht tuberkulösen Individuen sieht. Auch war die HI-Antikörperreaktion auf Vaccine gegen asiatische Grippe vergleichbar mit jener einer normalen Bevölkerungsgruppe mit ähnlicher Impfdosis.

Ausser bei zwei Personen schien die Virusinfektion die bei diesen Patienten bestehende tuberkulös Erkrankung nicht ungünstig zu beeinflussen. In einem der beiden Fällen liess sich der ungünstige Effekt innerhalb einer Zeit von 2 Monaten wieder beheben, und die Tuberkulose dieser Kranken hat sich anhaltend gebessert. Die Tuberkulose des anderen Kranken, hat sich fortgesetzt verschlechtert seit dem Beginn der Virusinfektion.

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Esophageal Replacement with a Reversed Gastric Tube

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Introduction

An operation will be presented which offers a physiological method of replacing the esophagus. Since this operation permits the entire esophagus to be replaced, an obstruction at any level of the cervical or thoracic esophagus can be by-passed by the reversed gastric tube.

The ideal surgical therapy for carcinoma of the esophagus is resection of the entire esophagus. Segmental resection of the esophagus may lead to incomplete removal of a carcinoma because it has been demonstrated that malignant cells extend longitudinally in the esophageal submucosa as far as eight centimeters from the primary lesion.[15, 19] Therefore, the reversed gastric tube operation is particularly advantageous in the treatment of carcinoma of the esophagus because normal gastrointestinal continuity can be restored after total esophagectomy.

The historical development of the reversed gastric tube operation has been described in previous publications.[5, 6] Mention should be made of the fact, however, that after this procedure was described in 1955, Dr. Dan Gavriliu of Bucharest, Rumania, wrote to inform the author that he had been performing this operation since 1951.[3] This author traveled to Bucharest in 1956 at the invitation of the Rumanian Academy of Medical Science, where he worked with Dr. Gavriliu and made a motion picture of the operation. Heimlich and Gavriliu then reported the results of the operation at the Meeting of the International Society of Surgery in 1957.[7]

Operative Technique

The entire esophagus is to be replaced. The abdomen is entered through a left subcostal incision. The tail of the pancreas is freed from its bed. The splenic vessels are ligated in the hilus of the spleen, preserving the origin of the left gastroepiploic vessels, and the spleen is removed. The blood passing through the splenic vessels is now directed into the left gastroepiploic vessels, which supply the greater curvature of the stomach (Figure 1A).

An incision is made into the greater curvature of the stomach through the anterior and posterior walls of the antrum, approximately five centimeters proximal to the pylorus. The incision is extended parallel to the greater curvature, at a distance of two centimeters, through both walls of the stomach, to a point high on the fundus (Figure 1B). The incised edges of the anterior and posterior walls of the stomach are sutured together forming the gastric tube and reconstituting the remainder of the stomach (Figure 2A).

From the Surgical Services of Montefiore Hospital (Cases 3, 4, 5 and 6) and Metropolitan Hospital (Cases 1, 2, 7, 8, 9 and 10).

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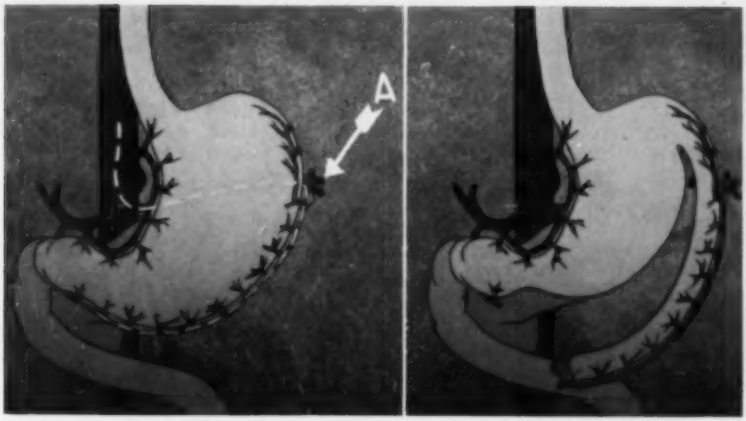

FIGURE 1A FIGURE 1B

Figure 1A: The spleen has been resected. (A), ligated splenic vessels. The dash line indicates the blood flow directed from the splenic vessels into the left gastroepiploic vessels to supply the greater curvature of the stomach.—*Figure 1B:* An incision has been made into the antrum, and extended parallel to the greater curvature. The gastric tube thereby formed remains attached to the stomach at the fundus.

An incision is made in the neck anterior and parallel to the left sternomastoid muscle extending upward from the suprasternal notch. A subcutaneous tunnel is created in the avascular plane anterior to the sternum, extending from the xiphoid to the incision in the neck. The gastric tube is drawn through the tunnel and is brought high in the neck, accompanied by its vascular supply, the left gastroepiploic vessels. The freed tail of the pancreas extends to the costal margin. The pancreas is accompanied

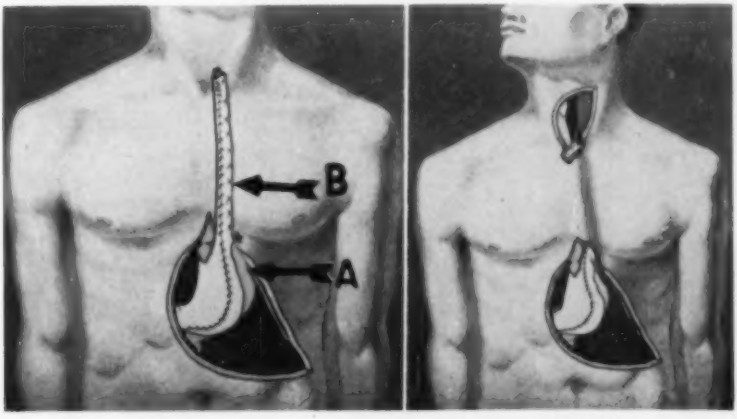

FIGURE 2A FIGURE 2B

Figure 2A: The gastric tube has been reversed and lies on the chest. The anterior and posterior walls of the stomach have been approximated, completing the gastric tube and reconstituting the stomach. A rubber catheter is seen emerging from the gastric tube. This catheter has been used as a mold on which the tube is constructed and it is removed at this time. The tail of the pancreas, (A), has been freed, and carries the splenic vessels to the costal margin. This permits the gastroepiploic vessels, (B), to accompany the gastric tube to the neck.—*Figure 2B:* The reversed gastric tube has been drawn to the neck through a subcutaneous tunnel.

by the splenic vessels from which the left gastroepiploic vessels originate. Thus, the vascular supply of the gastric tube is long enough to reach to the neck (Figure 2B).

Tne cervical esophagus is dissected free and transected approximately two centimeters distal to the pharynx. The distal end of the cervical esophagus is closed and is allowed to retract into the superior thorax. The reversed gastric tube is anastomosed end-to-end to the proximal cervical esophagus, restoring gastrointestinal continuity (Figures 3 and 4).

The functions of the esophagus can now be performed by the reversed gastric tube. If the esophageal obstruction is caused by a benign stricture or has been proved to be an inoperable carcinoma, it is not necessary to enter the chest. If a resectable carcinoma is present, a right thoracotomy incision is made and the entire esophagus is resected. The author has preferred to perform the thoracotomy at a second stage, 10 days to two weeks postoperatively.

The following details are of importance:

The left gastroepiploic vessels must be carefully preserved. Before this fact was fully appreciated, an attempt was made on one occasion to create a reversed gastric tube without this vessel, and the tube became necrotic. This serious error has not been allowed to recur.

The gastrocolic omentum is left attached to the greater curvature of the stomach, and is wrapped around the gastric tube as added protection for the suture line and the anastomosis.

A gastrostomy tube is inserted into the residual stomach after the gastric tube has been constructed, and is used to decompress the stomach for 24 to 48 hours. Thereafter the patient is fed through the gastrostomy tube for four to seven days, until he is able to eat an adequate diet. When the gastrostomy tube is removed, the opening seals within 24 hours. The

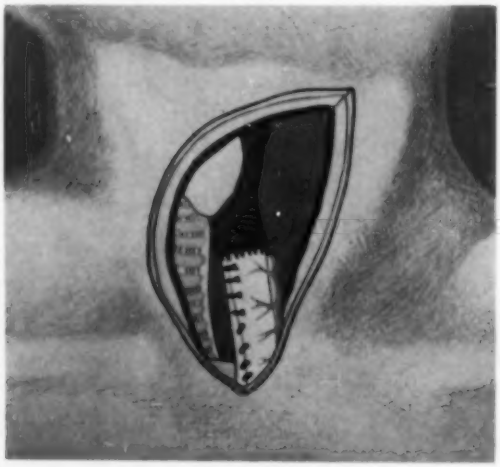

FIGURE 3: Through the incision in the neck, the cervical esophagus has been divided. Its distal end has been closed and has retracted into the thorax. The proximal end of the esophagus has been anastomosed end-to-end to the reversed gastric tube. The gastroepiploic vessels are seen accompanying the gastric tube.

presence of a gastrostomy prior to operation, which is usually the case in patients with benign strictures, does not interfere with the construction of the reversed gastric tube.

Case 1: J. H. (Metropolitan Hospital, No. 06-11-08). This 59 year old man had an extensive squamous cell carcinoma in the middle third of the esophagus (Fig. 5A). A reversed gastric tube operation was performed on April 19, 1957 (Fig. 5B). A small salivary fistula appeared in the neck on the 10th postoperative day and closed spontaneously one week later. Thereafter the patient was able to eat a regular diet. Radiotherapy was given because the lesion was not resectable.

The patient ate a regular diet until the day before he expired, on July 6, 1957. Postmortem examination revealed carcinoma of the esophagus with invasion of the trachea and aorta, and metastases to the liver. The reversed gastric tube was patent and the anastomosis was intact.

Case 2: P. G. (Metropolitan Hospital, No. 08-00-91). This 64 year old man had a squamous cell carcinoma in the middle and lower third of the esophagus. A reversed gastric tube was constructed on August 27, 1957, and anastomosed to the cervical esophagus. A small salivary fistula developed in the neck several days after operation and closed spontaneously in one week. Thereafter, he ate a regular diet.

On September 24, 1957, right thoracotomy was performed. The carcinoma was found to have infiltrated mediastinal structures and therefore was not resectable. A course of radiotherapy was given.

He had difficulty swallowing solid foods on two occasions postoperatively, at which time a partial stricture at the anastomotic site was dilated. In April, 1958, he was comfortable and was able to eat without difficulty (Fig. 6).

Case 3: B. V. (Montefiore Hospital, No. 8661). This 35 year old woman had a squamous cell carcinoma of the upper third of the esophagus (Fig. 7A). A reversed gastric tube was constructed on September 12, 1957. On September 23, 1957, right thoracotomy was performed. A carcinoma was present in the esophagus beneath the arch of the azygos vein, which had not extended beyond the esophagus. The entire esophagus, from the previously closed upper end to the cardia of the stomach, was excised with surrounding lymph nodes, none of which was enlarged. Microscopically, all nodes were free of tumor. The opening into the cardia was closed by inversion (Fig. 7B).

There was no postoperative difficulty. A superficial wound infection developed in the thoracotomy incision and healed rapidly after drainage. Fluids were taken by mouth on the fourth postoperative day, and she was advanced to a regular diet by the eighth postoperative day. She has gained 13 pounds since operation and at present is completely well (April 1958) (Fig. 8).

Case 4: L. W. (Montefiore Hospital, No. 93696). This 48 year old woman had received a course of radiotherapy for squamous cell carcinoma of the middle third of the

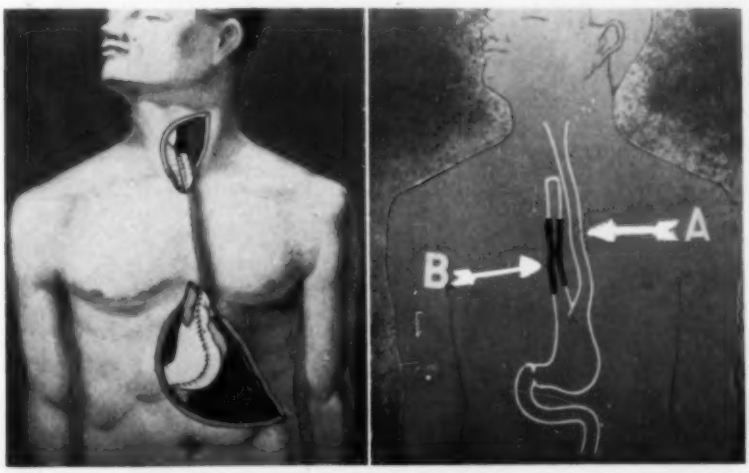

FIGURE 4, Completed operation: The functions of the esophagus can now be performed by the reversed gastric tube, (A). The diseased esophagus, (B), is nonfunctioning. It can be resected if an operable carcinoma is present, otherwise, it is left *in situ*.

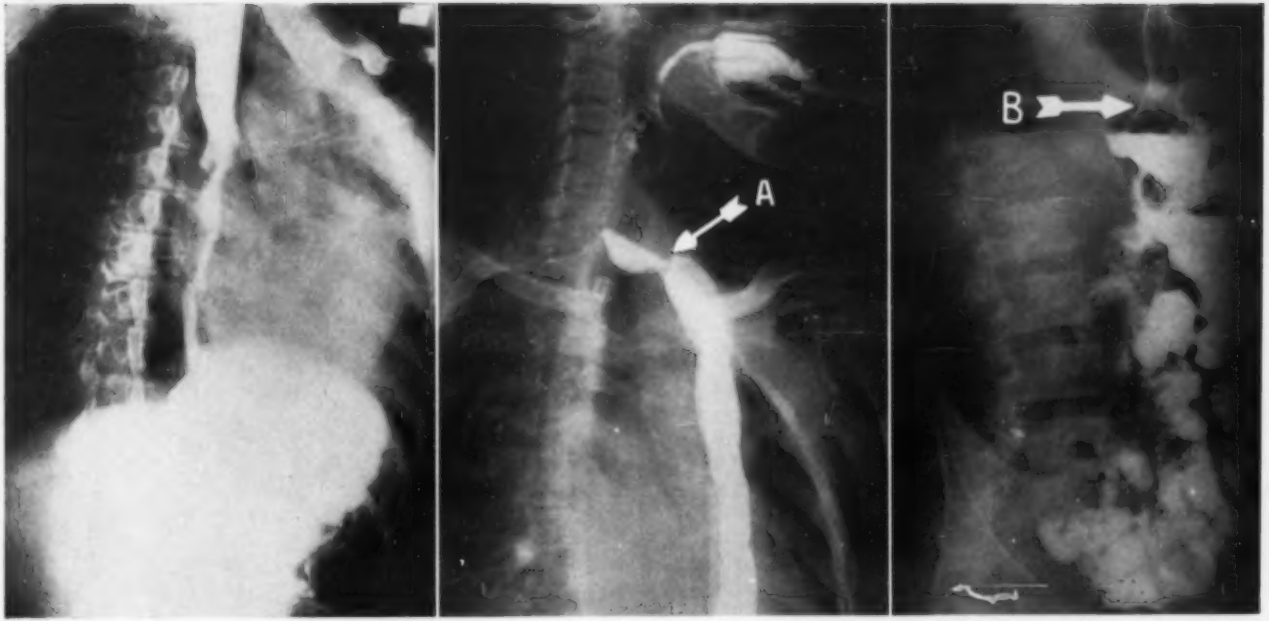

FIGURE 5A

FIGURE 5B

Figure 5A (Case 1): Preoperative esophagram, April 4, 1957: An extensive carcinomatous obstruction of the lower two-thirds of the esophagus is present.—*Figure 5B* (Case 1): Postoperative barium swallow through the reversed gastric tube. (A), the anastomosis between the proximal esophagus and the gastric tube. (B), is seen emptying into the large residual stomach in the abdomen.

esophagus at another institution. She had mitral and aortic valvular disease, and was in severe cardiac failure. Complete esophageal obstruction had recurred at the time of this admission, and because she could not swallow her own saliva, a reversed gastric tube was constructed on November 18, 1957. There was no complication. She ate a full fluid diet on the sixth postoperative day, and a regular diet thereafter. There was complete relief of salivary drooling. There is discomfort from the presence of the carcinoma, which is relieved by medication, but she continues to eat a regular diet (April 1958).

Case 5: E. D. (Montefiore Hospital, No. 92885). This 52 year old woman had a squamous cell carcinoma in the middle third of the esophagus and was only able to swallow liquids. A reversed gastric tube procedure was performed on November 11, 1957. On November 25, 1957, right thoracotomy was performed. The carcinoma had penetrated the wall of the aorta and was therefore not resected. Silver clips were placed at either end of the lesion to guide the localization of radiotherapy. Radioactive cobalt therapy was started on December 15, 1957. She ate well until the time of her sudden death on February 14, 1958. Autopsy revealed that death was due to hemorrhage caused by erosion of the carcinoma into the aorta. The gastric tube was intact and patent.

Case 6: D. S. (Montefiore Hospital, No. 90378). This 64 year old woman was admitted on December 12, 1957. Esophagram and esophagoscopic biopsy six months prior to this admission had established a diagnosis of squamous cell carcinoma of the upper third of the esophagus. Cobalt radiation therapy was given from July to September 1957 with partial relief of dysphagia. However, she continued to lose weight and, at the time of the present admission, had a recurrence of complete esophageal obstruction and regurgitated all foods and most liquids.

Esophagram, December 13, 1957: Markedly stenotic lesion in the upper third of the esophagus. The lumen of the stenotic area is slightly narrower than on the previous examination six months before.

Operation, December 16, 1957: Construction of a reversed gastric tube. There was no evidence of metastatic carcinoma in the abdomen or neck.

She had an uneventful recovery, and ate a regular diet from the sixth postoperative day. It was felt that an attempt to resect the carcinoma was warranted, despite the fact that she had received cobalt therapy four months previously.

Operation, January 7, 1958: Through a right thoracotomy incision, a total esophagectomy was performed. Although the lesion was a recurrent carcinoma, four months after cobalt therapy, it was not difficult to strip the esophagus from its bed. An

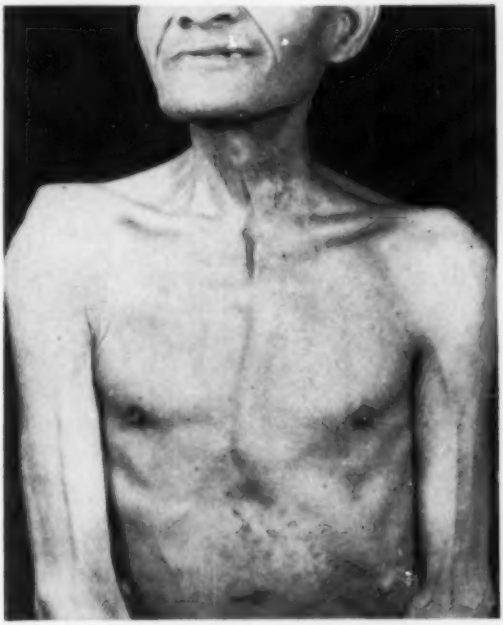

FIGURE 6 (Case 2): This patient had a nonresectable carcinoma of the esophagus. Eight months after the reversed gastric tube operation, he is still able to eat normally.

excellent cleavage plane was present and the carcinoma appeared to be well encapsulated by fibrous tissue. Pathological report of the resected esophagus: Squamous cell carcinoma extending out to the adventitial wall. The line of resection through the esophagus was free of tumor.

She had an uneventful recovery and was eating a regular diet by the third postoperative day. On the night of January 13th, six days after esophagectomy, and 25 days after the construction of the reversed gastric tube, she was walking in her room and tripped over a footstool, striking the right side of her chest. A severe intrapleural hemorrhage occurred. Thoracotomy revealed two fractured ribs which had lacerated an intercostal artery and had punctured the lung. Despite intensive supportive therapy she expired on January 24, 1958.

Case 7: G. P. (Metropolitan Hospital, No. 06-82-95). This 57 year old man had a squamous cell carcinoma of the middle third of the esophagus. A reversed gastric tube procedure was performed on January 6, 1958, at which time a large metastatic lesion was found surrounding the coeliac axis. The finding of this metastasis proved the incurability of the primary lesion, therefore unnecessary thoracotomy was avoided.

The patient had an uncomplicated postoperative course and by the seventh postoperative day, was eating a regular diet. He was discharged two weeks after operation and received radiotherapy as an out-patient. He was able to eat a regular diet until the day of his death, April 7, 1958. Autopsy revealed carcinomatosis secondary to carcinoma of the esophagus. The gastric tube was intact and patent.

Case 8: R. W. (Metropolitan Hospital, No. 06-65-96). This 61 year old man had had increasing dysphagia for one month. At the time of admission, on December 23, 1957, he could only swallow liquids and had lost a great deal of weight. He had been treated for hypertensive heart disease in the medical clinic for the previous six months.

Esophagram showed an indentation of the middle third of the esophagus. The proximal esophagus was dilated (Fig. 9).

Chest roentgenogram revealed an enlarged heart.

Esophagoscopy Report (Department of Otolaryngology), December 26, 1957: There is a gradual irregular narrowing beginning at the junction of the upper and middle

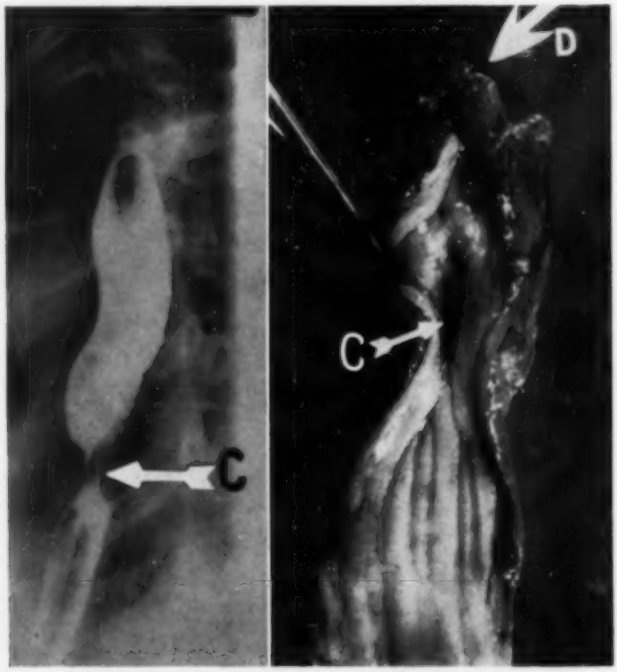

FIGURE 7A FIGURE 7B

Figure 7A (Case 3): Preoperative esophagram, August 20, 1957: Demonstrating partial obstruction due to carcinoma, (C).—*Figure 7B* (Case 3): Resected esophagus. (C), the carcinoma. (D), the distal end of the cervical esophagus, which was closed at the time the reversed gastric tube was constructed.

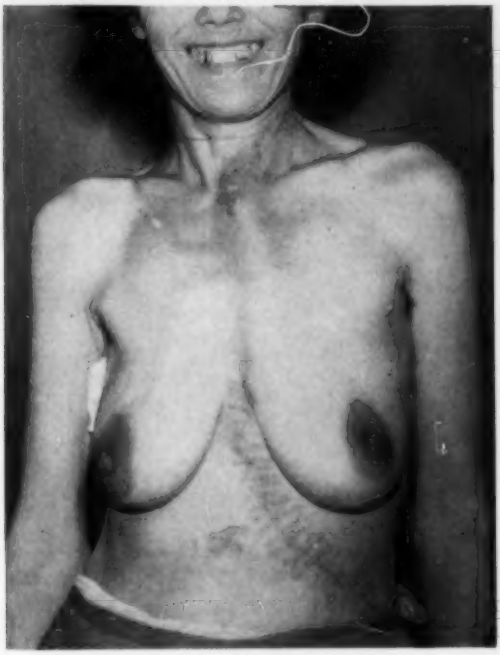

FIGURE 8A

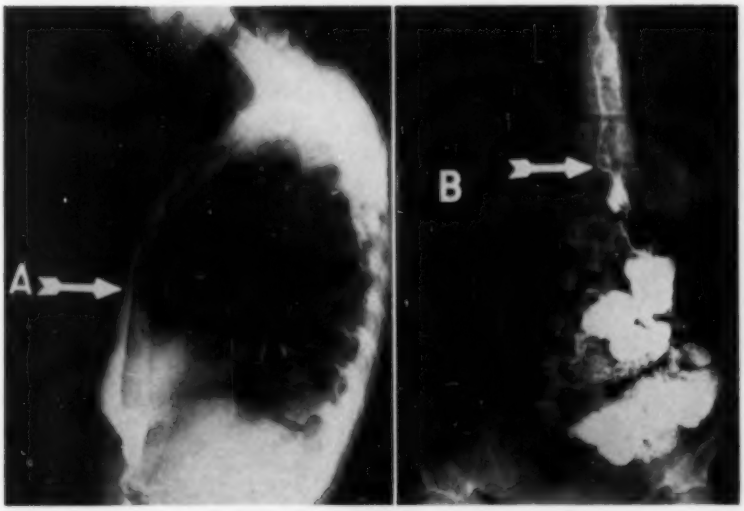

FIGURE 8B

Figure 8A (Case 3): Postoperative view of a thirty-five year old woman who had a reversed gastric tube operation followed by a total esophagectomy for carcinoma of the upper third of the thoracic esophagus.—*Figure 8B* (Case 3): Barium swallow through the reversed gastric tube. (A), the gastric tube, anterior to the sternum. (B), reversed gastric tube emptying into the residual stomach.

third of the esophagus and gradually increasing in severity so as to prevent further passage of the scope. There is no endoesophageal lesion seen. Impression: carcinoma of the esophagus.

Operation, January 9, 1958: Construction of a reversed gastric tube. The postoperative course was uncomplicated. Fluids and jello were eaten on the fourth postoperative day, and a soft diet on the fifth day. On the afternoon of January 14, 1958, the fifth day after operation, the patient, who had been ambulatory since the first postoperative day, was walking in the corridor and suddenly expired.

Autopsy Report: Lungs: Distal wedge shaped infarct, right lower lobe, fresh, hemorrhagic. The gastric tube was intact and patent. Cause of Death: Pulmonary infarct with vago-vagal reflex.

(It is of interest that the patient did not have carcinoma of the esophagus. The marked degree of esophageal obstruction was due to compression of the esophagus by an enlarged heart.)

Case 9: A. T. (Metropolitan Hospital, No. 08-42-40). This 62 year old man had a squamous cell carcinoma of the middle third of the esophagus. A reversed gastric tube procedure was performed on December 18, 1957. On January 2, 1958, the esophagus was resected through a right thoracotomy.

He had an uneventful recovery but was still unable to swallow. The obstruction appeared to be at the site of anastomosis between the gastric tube and the cervical esophagus. On January 21, 1958, an operation was performed to explore the anastomotic site in the neck. It has been the practice of this author to wrap the gastrocolic omentum around the anastomosis between the gastric tube and the esophagus. In this patient, the omentum was fatty and thick. The esophageal obstruction was found to be due to fat necrosis in the omentum, which had contracted around the anastomosis. The omentum was excised, the anastomotic site was resected, and a new anastomosis was made. The procedure was easily performed as the tube lay beneath the subcutaneous tissues in the neck.

The patient was known to be psychotic. His postoperative behavior after each operation was erratic. He pulled his gastrostomy tube out three times. On several occasions in the immediate postoperative period, he was found disoriented and drinking from a water faucet. After this last operation, a small salivary fistula developed in the neck. This drained for two weeks and closed spontaneously, after which he was started on a liquid diet. Shortly thereafter he was eating a regular diet. Radiotherapy was started on February 10, 1958, and directed to the site of the excised carcinoma. In March 1958, he had evidence of narrowing at the anastomotic site and required dilatation which was carried out on the ward. He has been eating well since that time.

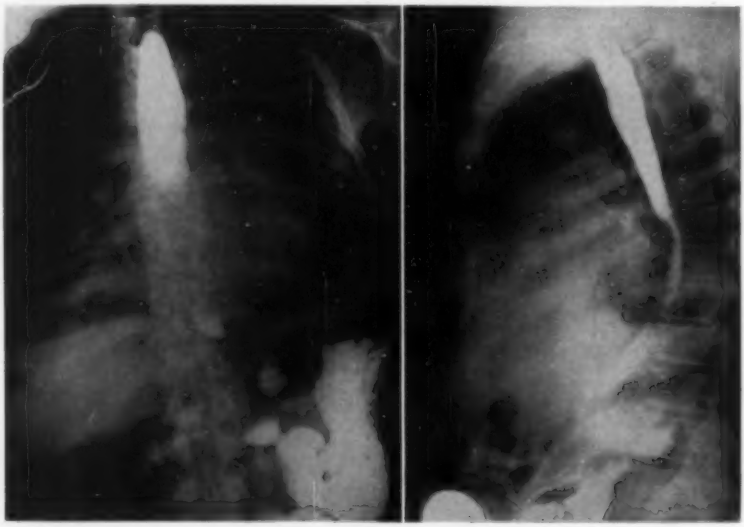

FIGURE 9 (Case 8): Preoperative esophagram, December 19, 1957: Demonstrating the marked esophageal constriction. Note the dilatation of the esophagus proximal to the obstruction which was thought to be due to carcinoma. The esophageal obstruction was later proven to be the result of compression of the esophagus by an enlarged heart.

Case 10: J. G. (Metropolitan Hospital, No. 07-03-37). This 45 year old woman had been unable to swallow solids or liquids since swallowing lye in a suicide attempt on May 7, 1956. A gastrostomy had been performed at the time of injury and she had been nourished by means of a gastrostomy tube for one and one-half years. She had been admitted to this hospital in June 1957, when an exploratory laparotomy was performed with the intention of constructing a reversed gastric tube. However, following the splenectomy, it was felt that the left gastroepiploic vessels had been inadvertently injured. Therefore, because it was known that under these circumstances a gastric tube will necrose (see Operative Technique), the operation was not performed and she was discharged. She was readmitted on January 2, 1958. It was felt that the reversed gastric tube procedure could be performed in the event that the gastroepiploic vessel had developed collaterals; otherwise, another means of esophageal replacement was contemplated.

Esophagram, May 29, 1957, showed almost complete obstruction of the thoracic esophagus and a second constriction in the cervical esophagus (Fig. 10A).

Operation, January 31, 1958, exploratory laparotomy: The left gastroepiploic vessels were adequate, and a reversed gastric tube was constructed and anastomosed to the cervical esophagus above the highest stricture. Although the stomach was markedly thickened and somewhat fibrotic, there was no difficulty in creating a gastric tube of adequate length to reach to the neck. The fact that the left gastroepiploic vessels were adequate may have been due to the development of collaterals. It is more likely that the experience gained by this surgeon in performing eight reversed gastric tube operations in the six-month interval since the first procedure on this patient, enabled him to evaluate more accurately the status of the vascular supply.

A small salivary fistula developed in the neck which healed spontaneously in several weeks. During this period she received nourishment by means of gastrostomy feedings. At present (April 1958) she eats a regular diet, and has gained six pounds since the reversed gastric tube operation (Fig. 10C).

Results

Ten consecutive patients have been presented in whom the reversed gastric tube procedure was performed. Every patient had marked esophageal obstruction; eight were due to carcinoma, and two caused by benign conditions. All were able to eat following their operations. The one death that occurred in the postoperative period was caused by pulmonary embolus on the fifth day after operation. He had been ambulatory since the first postoperative day, and began eating on the third day. It is of interest that his preoperative severe dysphagia had been due to compression of the esophagus by an enlarged heart.

Of the eight patients with carcinoma, three were resectable. Two of the three are living and show no evidence of recurrence four months and seven months after operation. The third had esophageal obstruction due to carcinoma that had recurred four months after a course of radioactive cobalt therapy. Despite this fact, resection of the esophagus was accomplished. Her death, six weeks after operation, was due to an accidental injury, unrelated to the surgery.

In the remaining five cancer patients, the reversed gastric tube operation was palliative because the carcinoma had already progressed beyond the possibility of resection. All five were able to eat normally after operation. Of the five, three did not have thoracotomy because metastatic lesions were found in the abdomen at the time the reversed gastric tube operation was performed. The other two patients showed no evidence of peripheral metastases. However, they were not resectable at the time of thoracotomy because there was extensive infiltration into surrounding tissues. Of the five non-resectable cases, two are living, five months and eight months after operation. Three expired from metastatic carcinoma within two to three months following operation.

Four of the 10 patients developed a small leak at the anastomosis, resulting in a temporary salivary fistula in the neck. In each case, the fistula

closed spontaneously in a short time. Two of the patients who had a salivary fistula developed a partial stricture at the anastomotic site. The strictures were dilated under local anesthesia on the ward. Because the anastomotic site is palpable beneath the skin of the neck, the danger of mediastinitis, which can result from perforation of an intrathoracic esophagus, does not exist. Following the dilatation, they have been able to swallow without difficulty.

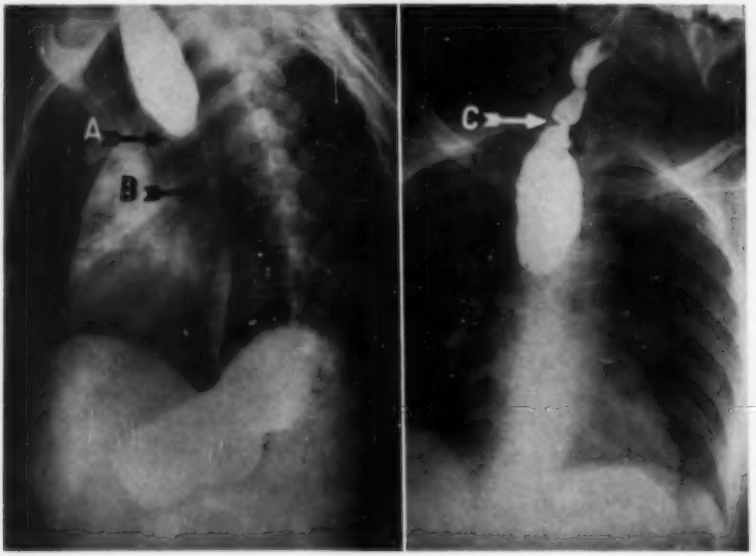

FIGURE 10A

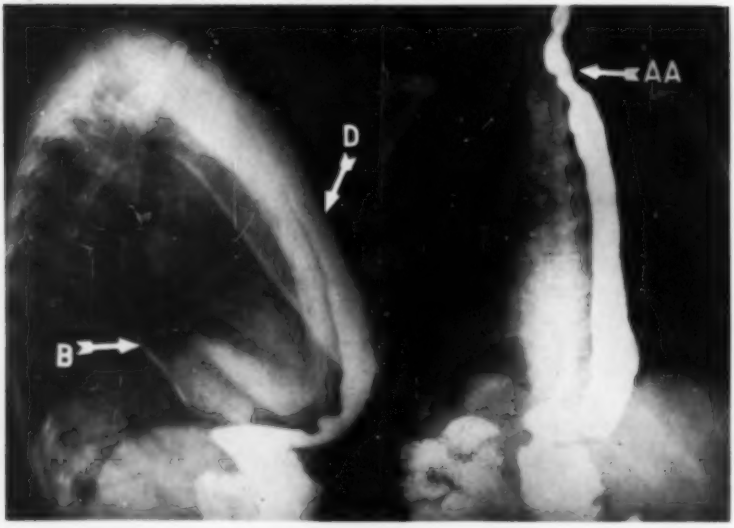

FIGURE 10B

One patient had a lye stricture of the esophagus and had been fed through a gastrostomy tube for one and one-half years. Since the reversed gastric tube operation, she has been able to eat a regular diet.

The general debility of the patients is illustrated by their preoperative status: Two had severe heart disease; five had extensive inoperable carcinomas, three of whom died from metastases within three months after operation; and two had recurrent carcinoma several months following a course of radiotherapy. It is encouraging that the operative procedure was well tolerated by these patients and that the complications were minimal. It is doubtful that they could have survived an extensive intrathoracic operation for the restoration of their gastrointestinal continuity.

Discussion

This operation offers a physiological means of replacing the entire esophagus, permitting total esophagectomy. The reversed gastric tube looks and functions like a normal esophagus. There is no intestinal organ or foreign material interposed between the proximal end of the esophagus and the stomach. The blood supply to the gastric tube is excellent. Weight and nutrition are maintained as the patient

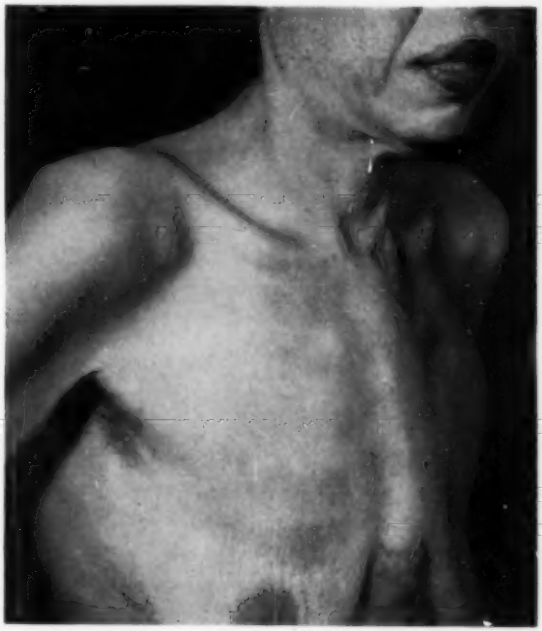

FIGURE 10C

Figure 10A (Case 10): Preoperative esophagram, May 29, 1957: An almost complete obstruction, (A), is demonstrated at the level of the aortic arch. A thin stream of barium is seen passing through the strictured esophagus, (B). Note the higher partial stricture, (C). It is not unusual to have two obstructions develop following the swallowing of lye. It is important that the anastomosis of a substitute esophagus be made above the highest stricture.—*Figure 10B* (Case 10): Barium swallow through the reversed gastric tube, (D). In the lateral film, the antesternal position of the gastric tube is evident. The anastomosis between the esophagus and the gastric tube, (AA), is higher than the uppermost stricture, (C), seen in Figure 10A. The barium which was swallowed has flowed up into the strictured esophagus, (B), which remains *in situ* with its upper end closed.—*Figure 10C* (Case 10): Postoperative view of the patient, illustrating the appearance of the reversed gastric tube which lies anterior to the sternum.

can eat all foods. In addition, four-fifths of the stomach remains in the abdomen and retains the normal storage function.

Esophageal replacement using the jejunum has been used successfully.[4, 12, 14] The difficulties encountered have been due to the inadequacy of the vascular pedicle, and ulceration of the jejunum.[16, 20] Recently, the colon has been used to replace the esophagus.[9, 11, 17, 20] This method was first reported in 1911.[5] The results appear to be encouraging and warrant further study, although the presence of freshly eaten food in the colon would seem to be an unnatural situation.

The stomach, by virtue of its excellent blood supply and mobility, has frequently been used to replace the esophagus.[1, 2, 15] The complications resulting from the presence of the stomach within the chest and the fatalities resulting from anastomotic leaks into the pleural cavity, have led Nakayama to recommend bringing the entire stomach to the neck subcutaneously.[10] However, it is the development of peptic esophagitis and strictures, due to the regurgitation of acid gastric juice when the esophagus is anastomosed to the fundus, that has inspired the search for a more satisfactory procedure.[11, 13]

Peptic esophagitis does not occur following the reversed gastric tube operation because the antrum, which does not secrete acid, forms the portion of the tube which is anastomosed to the esophagus. The proximal esophagus is, therefore, not sub-

TABLE I

Case No.	Age	Sex	Cause of Esophageal Obstruction	Location of Esophageal Obstruction	Follow-Up Period	Complications	Result
1.	59	M	Inoperable carcinoma	Middle third	3 months	Fistula in neck closed spontaneously	Regular diet. Died of extension of carcinoma
2.	64	M	Non-resectable carcinoma	Middle and lower third	10 months	Fistula in neck closed spontaneously. Two dilatations	Regular diet
3.	35	F	Resectable carcinoma	Upper third	7 months	None	Regular diet
4.	48	F	Inoperable carcinoma, had received radiotherapy	Middle third	5 months	None	Regular diet
5.	52	F	Non-resectable carcinoma	Middle third	3 months	None	Regular diet. Died of extension of carcinoma
6.	64	F	Resectable carcinoma, despite previous radiotherapy	Upper third	6 weeks	None	Regular diet. Died of trauma not related to gastric tube operation
7.	57	M	Inoperable carcinoma	Middle third	3 months	None	Regular diet. Died of extension of carcinoma
8.	61	M	Cardiac enlargement (not diagnosed preoperatively as the cause of obstruction)	Middle third	1 week	Pulmonary embolus	Soft diet before death from pulmonary embolus
9.	62	M	Resectable carcinoma	Middle third	4 months	Stenosis requiring reanastomosis. Fistula closed spontaneously. One dilatation	Regular diet
10.	45	F	Lye stricture	Middle third and cervical esophagus	3 months	Fistula in neck closed spontaneously	Regular diet

jected to the irritation of regurgitated acid gastric juice. Esophagitis has not been observed in patients followed three to five years after operation.[7] The author is of the opinion that either total esophageal replacement by a reversed gastric tube as described herein, or replacement of the lower part of the esophagus by a shorter reversed gastric tube could be utilized in the treatment of the following conditions: hiatus hernia with a short esophagus, chronic peptic esophagitis, bleeding esophageal varices, and severe or recurrent achalasia. The elimination of acid gastric juice regurgitation in these conditions should be of value in preventing esophagitis, stricture, and bleeding, which commonly recur following the present methods of treatment.

In the cases presented in this paper, the reversed gastric tube was brought to the neck subcutaneously, rather than intrathoracically or retrosternally. The advantages of the subcutaneous route are: 1. When an anastomotic leak occurs, it is a minor discomfort which heals spontaneously in several days or weeks. Should this complication occur following intrathoracic procedures, empyema results, which is almost always fatal. 2. The reversed gastric tube can be constructed and gastrointestinal continuity re-established without entering the chest. This is of particular importance when the patient is debilitated, as are the majority of these patients. In such cases, the esophagus can be resected at a second stage when the nutritional status has been improved. 3. When the esophageal obstruction is caused by a benign stricture or known inoperable carcinoma, it is unnecessary to resect the esophagus, and thoracotomy is avoided. Furthermore, the abdomen and neck can be explored at the time of the construction of the reversed gastric tube to determine whether metastatic carcinoma is present.

In a child or young woman with a benign stricture, where the cosmetic result is an important factor and the tissues are healthy, the author would consider placing the reversed gastric tube retrosternally.

SUMMARY

Ten patients have been presented in whom esophageal replacement with a reversed gastric tube has been accomplished. This operation provides a physiological means of esophageal replacement and offers the following advantages:

1. The reversed gastric tube looks and functions like a normal esophagus.
2. All foods can be swallowed in a normal manner.
3. The entire esophagus can be replaced.
4. Eighty per cent of the stomach remains in the abdomen retaining the normal storage function.
5. Peptic esophagitis does not occur because the antrum, which does not secrete acid, forms the portion of the reversed gastric tube which is anastomosed to the esophagus.
6. There is no intestinal organ or foreign material interposed between the proximal esophagus and the stomach.
7. The blood supply to the reversed gastric tube is excellent.
8. The reversed gastric tube is brought to the neck through a subcutaneous tunnel. If the esophageal obstruction is caused by a benign stricture or an inoperable carcinoma, thoracotomy need not be performed.

Acknowledgments: The author wishes to express his thanks to Helen Jacobson and Jane Heimlich for their assistance in preparing the text.

Note: The film "Esophageal Replacement With A Reversed Gastric Tube" can be obtained on loan by writing to: Professional Services Department, Baxter Laboratories, Inc., Morton Grove, Illinois.

RESUMEN

Se presentan diez enfermos en los que se ha hecho la substitución del esófago por un tubo gástrico invertido. Esta operación proporciona un procedimiento fisológico para reemplazar al esófago y ofrece las ventajas siguientes:

1. El tubo gástrico invertido se ve y funciona como un esófago normal.
2. Todos los alimentos pueden deglutirse de manera normal.
3. Se puede substituir todo el esófago.
4. El ochenta por ciento del estómago permanece en el abdomen reteniendo la cunción normal de captación.
5. No se observa la esofagitis péptica porque el antro, que no secreta ácido forma la porción del esófago invertido que se anastomosa al esófago.
6. No hay órgano intestinal o material extraño interpuesto entre el esófago proximal y el estómago.
7. La irrigación sanguínea del tubo gástrico usado, es excelente.
8. El tubo gástrico es llevado hasta el cuello a través de un túnel subcutáneo.

Si la obstrucción del esófago es causada por una estenosis benigna a por un carcinoma inoperable, no se necesita hacer una toracotomía.

RESUME

L'auteur présente les observations de 10 malades pour lesquels le remplacement de l'oesophage a été effectué grâce au renversement de l'estomac. Cette opération procure un moyen physiologique de remplacement de l'oesophage et offre les avantages suivants:

1. Le conduit gastrique inversé apparait et fonctionne comme un oesophage normal.
2. Toute la nourriture peut être avalée normalement.
3. L'oesophage entier peut être remplacé.
4. 80% de l'estomac demeure dans l'abdomen maintenant la fonction normale de stockage.
5. L'oesophagite peptique n'a pas lieu parce que l'antre, qui ne sécrète pas d'acide, forme la portion de tube gastrique inversé qui est anastomosée à l'oesophage.
6. Il n'y a aucun organe intestinal ou matériel étranger interposé entre l'oesophage et l'estomac.
7. La vascularisation du conduit gastrique inversé est excellente.
8. Le conduit gastrique inversé est amené au cou par un tunnel sous-cutané. Si l'obstruction oesophagienne est provoquée par une striction bénigne ou un cancer inopérable, la thoracotomie n'a pas besoin d'être pratiquée.

ZUSAMMENFASSUNGEN

Vorweisung von 10 Patienten, bei denen die Speiseröhre ersetzt worden war durch einen eingestülpten Magenschlauch. Diese Operation leistet Gewähr für einen physiologischen Weg des Ersatzes der Speiseröhre und bietet folgende Vorteile:

1. Der eingestülpte Magenschlauch erscheint wie ein normaler Oesophagus und funktioniert auch so.
2. Die ganze Nahrung kann in normaler Weise geschluckt werden.
3. Der ganze Oesophagus kann ersetzt werden.
4. 80% des Magens verbleiben im Abdomen und behalten die normale Speicherfunktion.
5. Es kommt zu keiner peptischen Oesophagitis, weil das Antrum, das keine Säure sezerniert, den Teil des eingestülpten Magenschlauches bildet, der mit dem Oesophagus anastomosiert.
6. Es gibt keine intestinalen Organe oder Fremdkörpermaterial das zwischen dem proximalen Oesophagus und dem Magen interponiert wäre.
7. Die Blutversorgung des eingestülpten Magenschlauches ist ausgezeichnet.
8. Der eingestülpte Magenschlauch wird mit dem Hals durch einen subkutanen Tunnel verbunden. Ist der Oesophagusverschluss durch eine benigne Striktur entstanden oder durch ein inoperables Carzinom, so braucht man keine Thorakotomie vorzunehmen.

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Discussion

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Dr. Heimlich has made a real contribution to the problem of esophageal substitution in cases of esophageal obstruction. It is of interest that of the 10 cases presented, while eight had carcinoma, four were men, four women. This is in variance with the usual sex distribution of this disease, even in a small series. He mentioned one significant point in regard to lye strictures, namely the high stricture at the cricopharyngeus that is usually overlooked in fluoroscopy because the barium is squeezed through this part of the esophagus so rapidly by the strong muscles of the hypopharynx. Bringing the tube as high as he does, overcomes this problem.

The need for an acceptable procedure to provide a reasonable substitute for normal deglutition in esophageal stenosis is apparent when one realizes the number and variety of operations designed for this purpose. So many have been described that it must be apparent that none is entirely satisfactory. The operation described by Dr. Heimlich has certain advantages over many others as he has indicated. Since our greatest problem in esophagology at the present time is the management of post-surgical strictures of the esophagus, we hope this procedure avoids this complication; but we are naturally somewhat skeptical of any new operation because of past experience.

In this operation the solution is again one of direct gastro-esophageal anastomosis with gastric juice secreting mucosa adjacent to esophageal mucosa. Dr. Heimlich indicates this objection is largely overcome by the fact that gastric secretion is minimal at the end of the tube sutured to the cervical esophagus. This raises a point as to whether peristalsis in the reversed gastric tube is reversed to the point of carrying gastric juice upward, especially when the patient is in the recumbent position. Such peristalsis, of course, would negate any advantage of decreased secretion of the mucosa at the site of anastomosis.

Dr. Heimlich mentioned that this operation could be used in malignant lesions of the distal esophagus merely by making the tube shorter. However, under such circumstances one must ask whether sufficient gastric mucosa adjacent to the lesion could be removed to avoid leaving residual carcinoma. Furthermore, in lye strictures one might be faced with a partially destroyed stomach when attempting this operation and an alternative plan of operation should be available when the procedure is contemplated.

In spite of these objections, we are most interested in this procedure, particularly since the patients who lived long enough postoperatively to judge whether a stricture would form at the site of anastomosis, only occasionally developed one. Certainly the most meticulous care must be used in making the anastomosis. I only hope time will provide additional evidence that the operation is effective.

The motion picture film presented in the film session of this meeting showed the operation performed in Rumania. This is a most valuable correlation of paper and film and demonstrates the advantage of this combined type of presentation.

The Clinical and Roentgenological Courses of Pulmonary Paragonimiasis†

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I. *Introduction*

On the chest x-ray findings and some clinical aspects of pulmonary paragonimiasis, one of the authors and his associates had first reported at the 44th annual meeting of the Formosan Medical Association in November 1951, and in previous papers.[1-3] More studies on the same subject have since come from Japan, Korea and elsewhere.[4-8]

There has been an explosive increase of new cases of lung fluke disease, especially during the period from 1948 to 1952, following the arrival of mainlanders in Taiwan after restoration of Taiwan to China in 1945. They were unaware of the association of paragonimiasis with the eating of raw or partially raw land-crabs, preserved in wine or brine, and freely indulged in this delicacy with untoward result. This unusual occurrence has enabled us to reevaluate the clinico-roentgenological findings of this endemic disease of hitherto only sporadic incidence here in Taipei, and made it possible for us to call attention of the medical profession to the fact that the chest x-ray film findings of pulmonary paragonimiasis include many manifold changes which are at times highly characteristic, instead of showing "very little change" from the normal, as formerly described.[9, 10] We may find:

a. well or moderately well defined nodules often with small central translucency, (Figs. 2B and 5)
b. ill-defined hazy transient opacities completely reversible or with residual nodules, (Figs. 3, B and C; 4A; 10, A, B and C)
c. ring shadows
d. pleurisy, often bilateral, (Fig. 2A)
e. spontaneous pneumothorax, often with effusion, (Figs. 1A and 6)
f. calcifications
g. increased and/or irregular lung markings, (Fig. 1C)
h. slight dilatation or irregularity of bronchial tree, (Fig. 7)

and in the previous paper the incidence of these abnormalities was tabulated. We also suggested that if closely followed from the onset of the disease, each new patient may show every conceivable type of clinico-roentgenological abnormality which is seen at various times in the course of the infection. Very naturally, therefore, our next interest is concentrated in the long range follow-up of our cases in order to understand the entire clinical as well as roentgenological course of the disease.

Up to now, there have been since 1947 more than 300 proved cases of pulmonary paragonimiasis recorded in the Medical Department of National Taiwan University Hospital, including five autopsy cases who died

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of cerebral infection with paragonimus flukes. Of these, 40 cases have been closely followed-up from three to 10 years. In a few cases, clinical studies have been feasible from the beginning of the disease; knowing the date of infection, the first abnormality of chest roentgenography, the date on which parasite ova were first found and the following clinico-roentgenological findings, as if we were observing some human experimental cases. With these clinical materials, our observation has been intense and long enough to let us understand the whole clinical picture of the lung fluke disease and to clarify some hitherto undisclosed aspects, especially on the clinico-roentgenological findings in its entire course. Armed with those facts, we would like to present this paper, bearing in mind that most of our material consists of adults, more than two-thirds of whom were men.

II. *Life History of Paragonimus Westermanii*

Before we enter our study it is worth while to mention briefly the life history of *paragonimus westermanii* as studied by animal experiments.

A miracidium develops in 15 to 20 days inside of the parasite ovum in sputum or feces of a patient. It hatches in the water and enters a snail of the genus Melania, the first intermediate host. It develops in about 60 days into sporocyst and rediae and then cercariae. The cercariae bore into freshwater crabs of genus Potamon or Ericocheir, the second intermediate host, and become meta-cercariae. In the second intermediary the meta-cercariae encyst in the muscles, gills and viscera. When infected fresh water crabs are taken raw or undercooked, the cyst wall of metacercariae is digested in the stomach and the adolescercaria (larvae) emerges which passes through the intestinal wall, traverses the abdominal cavity, penetrates the diaphragm and pleura and reaches the lungs in about four weeks. It will take, thereafter, another five weeks or more for the larvae to become mature, to form cystic cavity in the lungs and to ovulate.[11]

In addition to this regular route to pulmonary infestation, the larvae may migrate to diaphragm, mediastinum, pericardium, liver, adrenals, omentum, testis and scrotum to cause heterogenous infestation. The larvae may also migrate along the perivascular connective tissue to the central nervous system, spine, brain or orbit to cause often fatal manifestations.

III. *Clinico-roentgenological Course of Pulmonary Paragonimiasis*

Basing on our clinical observation we conclude that it is reasonable as well as advisable to divide the entire clinical course of pulmonary para-

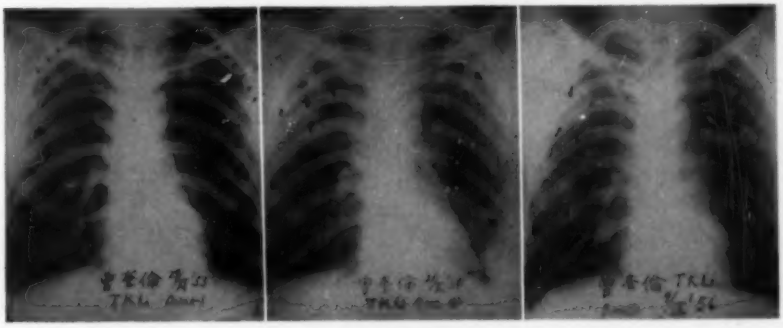

FIGURE 1A FIGURE 1B FIGURE 1C

TABLE I—FIRST CLINICAL SYMPTOMS (IN 45 CASES)

Symptoms	Cases	Interval Between Infection and Onset of Symptoms	
		Range (months)	Average (months)
Epig. or Abd. Pain.	8	1 - 5	2.25
Chest Pain.	18	1 - 9	4.08
Subst. Discomfort	1	-	2.00
Cough	22	1 -14	4.23
Creeping Tumor	5	2.5- 9	4.70
Bloody Sputum	41	1 -20	5.05

gonimiasis into the following three stages, that is, stage of migrating larvae, stage of mature worms and stage of recovery.

1. *Stage of Migrating Larvae*

Clinically, we would like to define this stage as the period from infection to the first demonstration of ova in the sputum. Although, the majority of our cases come to us with chief complaints of recurrent bloody sputum and parasite ova were proved to be present at the first visit, not a few patients were observed at or could be traced back by the clinical history to this early stage. History taking of 45 cases who had single infection and could give reliable date of clinical onset discloses that the first clinical symptoms after infection can be one or more of the following; epigastrial or abdominal pain, chest pain, cough, bloody sputum, and creeping tumors. (Table I).

Among these, abdominal pain or epigastralgia can be the first clinical manifestation after infection, and due to the migrating larvae in the abdominal cavities. Symptoms suggesting pleurisy may be the first or the second manifestation which are obviously caused by the migrating larvae in the pleural cavities. Fever is usually absent or may be slight.

In correlation with these clinical symptoms, the first chest x-ray film manifestation of pulmonary paragonimiasis is pleurisy with or without effusion which may be accompanied by spontaneous pneumothorax (Case 1) and soft pulmonary infiltrations (Case 3). Pleurisy at this stage of the disease is often bilateral (Cases 1, 2, 3 and 5) in contrast to that of tuberculous origin which is usually unilateral. Spontaneous pneumothorax and pulmonary infiltration, if any, may subside quickly, but pleurisy

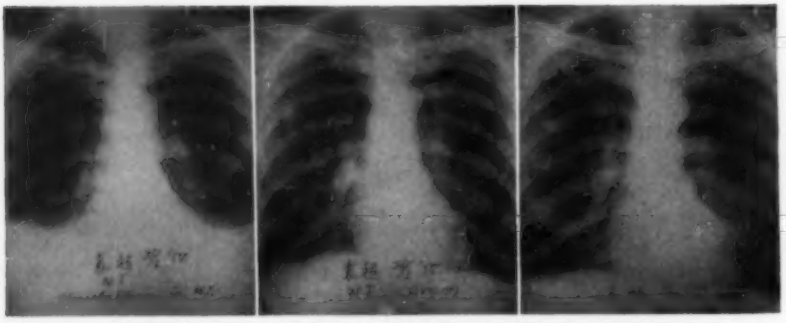

FIGURE 2A FIGURE 2B FIGURE 2C

usually remains longer. The former conditions, therefore, are much less often proved clinically. The effusion, if aspirated, consists of thin, yellowish, transparent exudate with many eosinophils (Case 2).

The time interval between infection and the first clinico-roentgenological manifestation is around one month at shortest but can be much longer (Table I). Knowing the developmental history of the parasite in the experimental animals, it is justifiable to say that reactions of this sort are caused by the larvae penetrating the diaphragm and/or the visceral pleura to gain access into the lungs, or migrating in the pleural cavities.

After the larvae enter the lungs, they may immediately settle down in certain places of the lungs to become mature worms or may migrate in the lung for an indefinite period of time before they finally do so. This is supported by the fact that the time interval between infection and parasite ova first found in the sputum is variable, ranging from three months to almost one year, and that in some cases we may observe the following clinico-roentgenological findings.

The clinical symptoms in the period of migrating larvae in the lungs are irritable cough, chest pain, general malaise with or without slight fever. Bloody sputum, not the characteristic chocolate-colored sputum, but

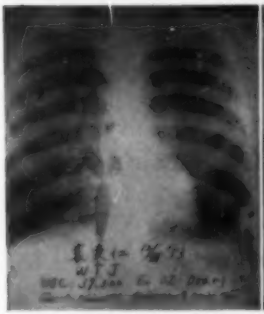

FIGURE 3A

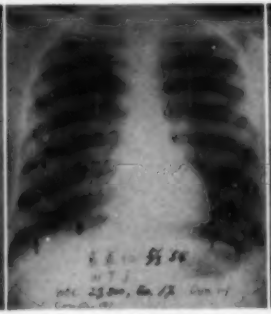

FIGURE 3B

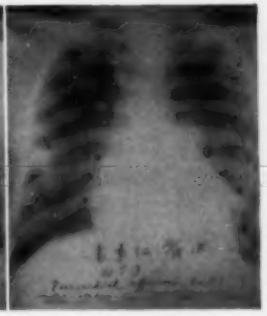

FIGURE 3C

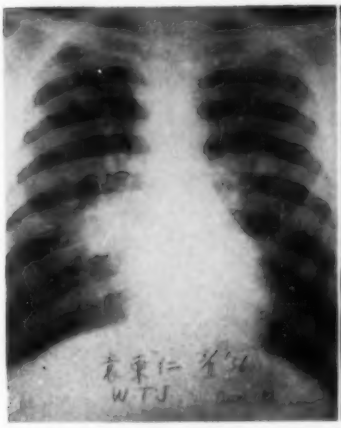

FIGURE 3D

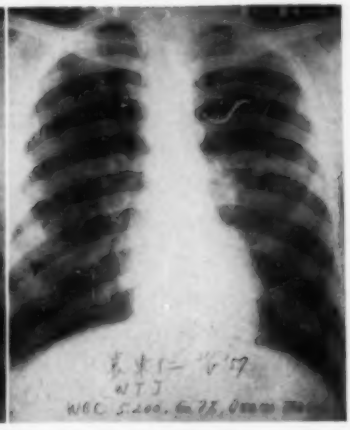

FIGURE 3E

blood-streaked sputum may be seen. The corresponding chest x-ray film finding consists of the migratory, transient soft pneumonic or bronchopneumonic shadows, which can be seen in any part of the lung fields (Case 3, and Fig. 10). In comparison with ordinary bacterial pneumonic or bronchopneumonic lesions, they are more irregular in size, form, and distribution of densities. They do not show lobular or segmental distribution. These shadows are changeable. In a week or two, they disappear from one place, remain the same in another and/or develop new lesions in the previously normal lung fields. These inconstant manifestations may last for several weeks or months. It is reasonable to assume, as mentioned, that they are caused by the migrating larvae in the lungs before they reach maturity and occupy permanent sites of settlement in the lungs. Pericardial effusion, although uncommon, is also observed at this stage (Case 3). In cases without vigorous migration of larvae within the lungs, these transient pneumonic shadows as well as the clinical symptoms may, of course, not be observed.

Physical signs of the chest are those of pleurisy, and/or pneumothorax, but abnormal signs in the lungs are lacking even though the chest x-ray

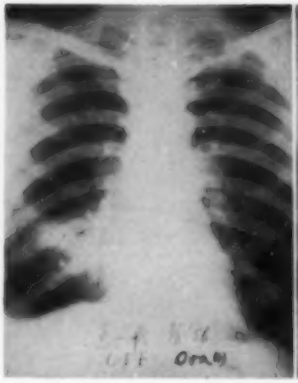

FIGURE 4A

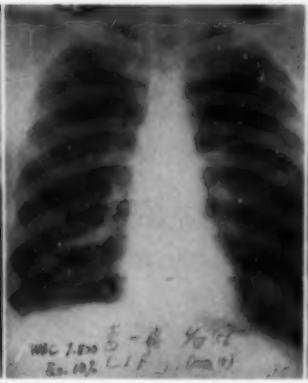

FIGURE 4B

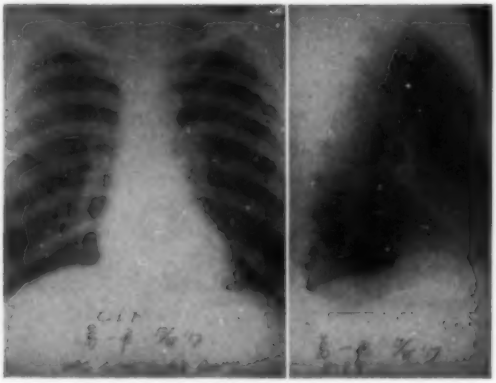

FIGURE 4C

films show abnormal densities. Leukocytosis of moderate or marked degree (may reach more than 30,000) with high eosinophilic count (may be up to 80 per cent) are common at this early stage and are usually more and higher than at a later time. Increased sedimentation rate of varying degree is also common. At this stage, of course, one cannot find parasite ova either in the sputum or in the effusion. The differential diagnostic clue from pleurisy, pneumothorax, or pneumonitis of other origins is the presence of high eosinophilia in the peripheral blood as well as in the effusion, its often bilateral manifestation, the transitory character of the x-ray shadow, lack of fever and above all the past history of partaking of raw or semi-cooked land-crabs. From roentgen-diagnostic view point, it is usually difficult to tell the nature of the abnormality with a single chest x-ray film at this stage, but with a series of chest x-ray films taken at short intervals, we are often able to predict the correct diagnosis before the parasite ova can be discovered in the sputum. If, in addition, there is a positive history, suggesting symptoms including the presence of creeping tumors and/or laboratory data available, the diagnosis can be made with certainty before parasite ova are demonstrated. Diagnostic value of paragonimus antigen in these early stages has yet to be studied. The time interval between infection and the detection of parasite ova in the sputum, from our experience, varies from person to person, ranging from about three months at least to almost one year in some cases. The time interval is longer than that observed in animal experiment. This observation may be explained by the facts that:

a. In the human body the young worms take a longer time to become mature than in the animal body.
b. There is a variable period of time for the migration of the larvae, as mentioned.
c. There is a different time interval for the evacuation of produced ova in the air way.

In brief, the clinical observations also indicate, as proved by the animal experiments, that after infection the larvae penetrate the intestinal wall

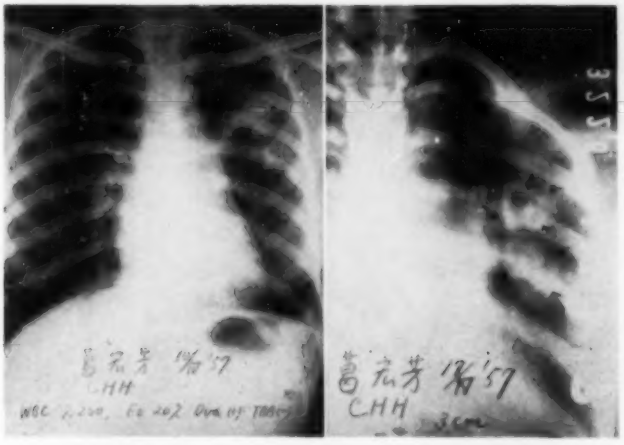

FIGURE 5A FIGURE 5B

and migrate in the abdominal cavity, then penetrate the diaphragm and migrate in the pleural cavities, finally penetrate the visceral pleura and migrate in the lungs before they settle down in certain places to become mature worms. This migrating process may in some cases cause the clinico-roentgenological findings of abdominal or epigastric pain, chest pain, pleurisy with or without pneumothorax and transient pneumonitis with chief complaints of blood-streaked sputum and irritable cough. The duration of the migrating process is, judging from our clinical observation, variable, ranging from three months up to almost one year.

2. *Stage of Mature Worms*

This stage refers to the period during which the mature worms are alive in the lungs. Clinically, however, we may define this stage as the period when parasite ova can be found in the sputum.

The main clinical symptom of well-established cases is recurrent bloody sputum, characteristically chocolate-colored with a peculiar odor, especially after physical exertion. Cough may be present but fever is usually absent except when the patient has perifocal infection. Malaise and loss of body strength are common. The general condition, however, is usually not impaired and physical signs in the chest are lacking except when secondary pleurisy or pyothorax and/or pneumopyothorax develops, which will be mentioned later.

The most characteristic chest x-ray film findings for pulmonary paragonimiasis which can be observed at this stage and by which we are now often able to make a diagnosis with a single chest x-ray film is the presence of well or fairly well-defined patches or nodules, having very often small, about 0.5 cm. in size, central translucent area or areas (Figs. 1B; 2B; 3, D, and E; 4B and 5). We would like to call them "cystic nodules or patches," which are best seen by tomogram (Fig. 5B) and certainly representing the "worm burrows" (Fig. 8). This viewpoint may be justifiably supported by resected surgical specimens.[12-13] These nodules or patches may be seen in any part of the lung, more often bilateral, multiple and located closely together. They are variable in size, ranging from 1 cm. to 5 cm. or so; their sizes and densities are subject to change, growing small or enlarging or

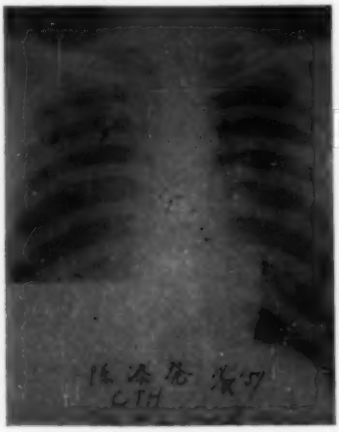

FIGURE 6

even to disappear completely and also may reappear, depending upon the degree of pericystic reaction (Cases 1, 2, 3 and 4). In previous reports we have stated that "they do not disappear completely although they may change their size and density," but with more cases and longer follow-up we find these nodules do sometimes disappear completely from the ordinary P-A view chest x-ray film although they may reappear at a later time. Considering the histological findings of "worm burrow" (Fig. 9), we can only explain this by the changing degree of tissue or inflammatory reactions of the worm burrows, because changing place of the mature worms in the lungs is believed to be limited even though our pathologists are inclined to opine that they may do so, either actively or passively, basing on the microscopic study which shows that the parasite ova can be traced at different locations. Nevertheless, the central translucent area represents the cystic space where the worm is located, and shadow casting wall represents fibrotic wall with variable amounts of caseous material, by-products of the worms, and cell infiltration or inflammatory reaction surrounding the cyst. The degrees of the reaction are changeable and the by-product of the worms may be evacuated from time to time. The size as well as the density of the "cystic nodules or patches," therefore, depends upon the number of the burrows present close together and intensity of tissue, and/or inflammatory reactions surrounding the worm cyst. If the reaction is marked, especially in cases when many burrows are situated near each other, the patch becomes fairly big and central translucency may be obscured. If the reaction is moderate, we may find typical "cystic nodules" and if it is slight or minimum, consisting only of thin fibrotic tissue or even milder, we may find small thin walled cystic cavities which sometimes can only be seen by tomogram. This may be one of the reasons why the chest x-ray films appear essentially normal at one time or another in chronic cases with positive ova found in the sputum. The biggest cystic cavities we have seen are about 3 cm. in diameter. They may be produced by the breakdown of burrows, located adjacent to each other or may be caused by some obstructive bronchial mechanism.

Bronchographic changes attributable to the parasite infection are usually lacking, but in some cases, localized dilatation of the bronchi around

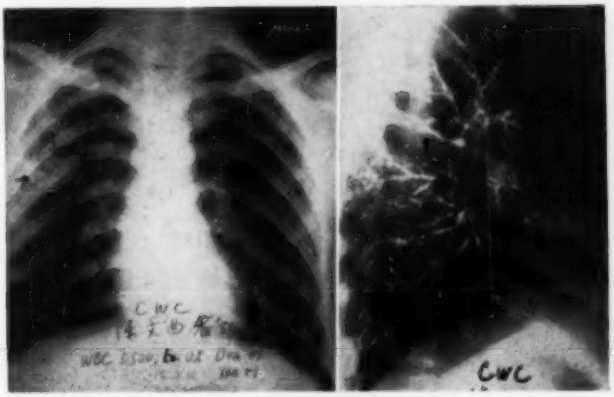

FIGURE 7

the "cystic nodules" has been demonstrated (Fig. 7). This may explain the reason why frank hemoptysis is sometimes present in chronic or in even healed cases.

In contrast to the pleurisy or seropneumothorax seen in the first stage, we can observe another form of pleurisy with effusion, often encapsulated, pyothorax, or pneumopyothorax in this stage (Cases 1 and 4, Fig. 6). These complications arise when worm burrows are situated near the pleura, when the worms are actually present in the pleural cavity, and/or when bronchopleural fistula is formed. The exudate in these cases is usually turbid and often purulent or chocolate-colored instead of being transparent and the condition lasts longer in comparison with the same conditions observed in the first stage. Eosinophilic leukocytes are usually rich and parasite ova may be found in the effusion on rare occasions (Fig. 6); four cases in our material.

White blood cells and eosinophilic count in peripheral blood in chronic stabilized cases are usually within the normal limits or may be slightly increased. With increasing pericystic reaction or complicating pyo- or pneumopyothorax they may increase moderately. Eosinophils in complicating pleural effusion are abundant. Sedimentation rate is also normal.

Diagnosis of pulmonary paragonimiasis at this stage is usually easy; it can be suspected by careful history taking, recurrent chocolate-colored sputum without impairment of general conditions, lack of abnormal physical signs from lung parenchym, positive antigen test, and can be easily proved by positive ova in the sputum at the first visit without chest x-ray film examination. As we said, characteristic cystic nodular shadows of unusual distribution lead us to suspect the correct diagnosis on a single chest x-ray film, but for the inexperienced, the existence of these abnormal shadows may prevent him from carrying out adequate sputum examination and lead to a misdiagnosis of pulmonary tuberculosis. In fact, many of our cases had had tuberculosis chemotherapy for sometime before they came to us. In cases with unilateral, atypical cystic nodular or shadows limited to the clavicular or subclavicular regions, the roentgenological

FIGURE 8

FIGURE 9

differential diagnosis from pulmonary tuberculosis is certainly difficult. Coexistence of paragonimiasis and pulmonary tuberculosis, moreover, is by no means rare in Taiwan.

In brief, in the stage of mature worms, the typical clinical manifestation is recurrent chocolate-colored sputum with positive parasite ova, and the corresponding chest x-ray findings is cystic nodular or patchy shadows of unusual distribution. X-ray manifestation of "cystic nodules or patches" becomes first defined several months after infection, possibly shortly before the appearance of parasite ova. Thereafter, as long as the parasite ova are found, in other words, as long as the parasite is alive, the above mentioned changeable chest x-ray findings can be seen and secondary pleurisy, pyothorax or pneumopyothorax may arise as a complication in some cases. In turn, we may say that so long as these x-ray film patterns persist, the parasite should be regarded as alive even when the ova cannot be found for some time.

We now believe that in the long run no case of pulmonary paragonimiasis can be entirely devoid of abnormal chest x-ray findings. In some chronic cases, however, with positive ova in sputum, the single ordinary P-A view chest x-ray film may at some period show negative findings. This fact can be explained by the following reasons;

a. the lesions are hidden by the mediastinal hilar or diaphragmatic shadows.
b. the cystic nodules have little surrounding reaction so that they only cast a small cystic wall which can be easily overlooked in a ordinary chest x-ray film.
c. or both.

3. *Stage of Recovery*

The infesting parasites will sooner or later die either spontaneously or following treatment. The resultant clinical pictures are disappearance of recurrent bloody sputum, gain of body strength and negative ova ascertained by repeated sputum examinations. The only episode which can occur in rare cases after cure is frank hemoptysis attributable to the bronchiectasis mentioned above. Pulmonary paragonimiasis is said to be cured spontaneously within 10 years even without active treatment, as the longevity of the parasite in the human body is limited. We know, however, of three cases having positive ova lasting for more than 10 years without any known reinfection.

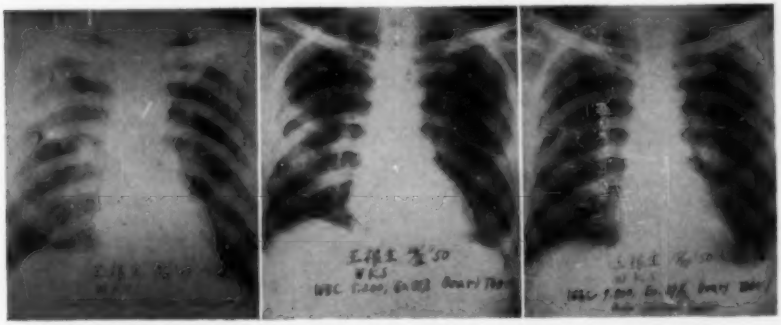

FIGURE 10A FIGURE 10B FIGURE 10C

Eventually, chest x-ray films after recovery show complete absorption, tiny fibrotic or hard nodular shadow (Case 4) and even calcified spots at the place where cystic nodular shadows previously existed. This is proved by autopsy of cases who have died of other disease. It is our impression, therefore, that as long as the cystic nodules or cystic walls are found by the shadows they cast on the chest x-ray films, the worms are alive, and that once the parasites died, the worm burrows will be replaced by fibrotic tissue and eventually calcium may be deposited.

After cure, all the laboratory data are within the normal limits. From the chest x-ray findings, nobody can tell the past history of having suffered from lung fluke disease. By our experience with limited number of cases the antigen test remained positive at this time.

IV. *Extrapulmonary Infestation*

As extrapulmonary infestation, we have observed creeping tumors in the subcutaneous tissue, as well as the pericardial, intestinal, peritoneal, testis and cerebral manifestations. They may be the only clinical signs but are more often accompanied by pulmonary infestation. Extrapulmonary infestation as well as the primary pleurisy was often seen during the period between 1948 and 1952 when new cases were prevalent, but has become much less frequent in recent years. This fact can be easily understood when it is well known that these manifestations usually take place in a comparatively early stage.

So far, we know of eight fatal cases, all due to cerebral infestation, of which five were autopsied and on three of whom Dr. W. S. J. Lin of the Pathological Department has reported.[14] The clinical symptoms of cerebral involvement are those suggestive of epilepsy, brain tumor or meningitis. They generally appear within one year after infection, the longest being 1.5 years. On the extrapulmonary infestation we would like to refer to the paper written by Dr. C. P. Kuo,[15] reporting six cases of his own with review of the literatures.

V. *Treatment*

For the treatment of pulmonary paragonimiasis we have tried emetine hydrochloride, either alone or with sulfa drugs or antibiotics, antimony preparations, chloroquine, hetrazan and other preparations. Intrabronchial administration of emetine with hyaluronidase as well as that of Rivanol have also been tried. None of these preparations has so far given satisfactory results.

Emetine hydrochloride still seems to be the drug of choice. Some cases do respond to it well; after one course of treatment or two, all the clinical symptoms as well as parasite ova disappeared and never relapsed. Generally speaking, however, the effect is only symptomatic and temporary. It is our impression that patients who are not cured by one or two courses of emetine administration, will never respond to subsequent courses of the same drug.

VI. *Representative Case Reports*

Case 1: T. K. L. 36 year old man. Taiwanese.

Crabs eaten: Once in October 1953.

First clinical symptoms: Chest pain at end of November 1953 and bloody sputum May 1954.

Clinico-roentgenological follow-up: November 27, 1953—Bilateral spontaneous seropneumothoraces (Fig. 1A). Ova (—) in sputum. June 23, 1954—Cystic nodular lesion in left upper lung with bilateral pleural reactions. Ova (+) in sputum. August 23, 1954—Left, as before. Cystic lesion appeared in right upper lung field. October 21,

1954—More cystic nodular lesions in the right upper. Encapsulated pleurisy with more effusion developed on the left chest (Fig. 1B). January 4, 1955—Regression of cystic lesions in the right upper lung, others no change. March 17, 1955—Reappearance of hazy density in right upper lung field. Others, no remarkable change. May 21, 1955—Cystic hazy densities in right upper lung. Fibrotic nodular lesion in left upper lung. Bilateral encapsulated pleurisies. Pleural tapping (—). White blood cells 8,450, Eosinophil 6 per cent, Ova (+) and Tubercle bacilli (—) in sputum. May 30, 1955—Decreasing pericystic infiltrations, others as before. June 6, 1955—Bronchography negative. November 10, 1955—Pleurisy clear out. Lipiodol rest (+). September 7, 1956—Cystic lesions in both upper lung. New nodular lesion appeared in the right lower lung (Fig. 1C). Bloody sputum (+). April 15, 1958—Almost as before. Ova (+) in sputum.

Treatment: Emetine injection, more than 30 ampules (40 mg.). Rivanol solution (500x) intrabronchially in May 1955.

Result: Still complains of recurrent bloody sputum and general malaise (in June 1958).

Comment: Began with bilateral seropneumothoraces one and a half months after infection. Ova first found several months thereafter when the chest x-ray film showed cystic nodular shadows. Changeable cystic nodular or cystic hazy shadows thereafter. Bilateral encapsulated pleurisies of later stage appeared which lasted about one year. Resisted emetine as well as Rivanol treatment.

Case 2: W. T. 50 year old man. Kiangsunese. Father of Case 3.

Crabs eaten: Once only in October 1953.

First clinical symptoms: Abdominal pain in early November 1953. Chest pain (pleurisy) January 15, 1954.

Clinico-roentgenological follow-up: January 21, 1954—Bilateral pleural effusion (Fig. 2A). Eosinophil 46 per cent in pleural effusion. February 17, 1954—same findings except small density appeared in the right upper lung. White blood cells 19,150, Eosinophil 73 per cent, Ova (—) in sputum. January 28, 1955—Pleural effusion disappeared (Fig. 2B). Cystic nodules in right upper and middle lung fields. Ova (+) in sputum. Complained of bloody sputum. March 20, 1955—Cystic nodule near the right hilum disappeared. New one appeared in right upper lung field. June 13, 1956—Bronchopneumonic densities in both lower lungs. Pleural reaction in the left chest. September 5, 1956—Bronchopneumonic densities disappeared. Cystic densities decreased in number. Ova (+) in sputum. June 6, 1957—Cystic nodular densities with increased perifocal infiltrations (Fig. 2C). White blood cells 11,100, Eosinophil 12 per cent, Tubercle bacilli (—) and Ova (+) in sputum. April 23, 1958—Cystic nodular shadows with less perifocal infiltrations in both lung fields. White blood cells 7,800, Eosinophil 1 per cent, Ova (+) in sputum.

Treatment: Emetine combined with sulfa drug. Tripaflavin injection.

Result: No cure.

Comment: Began with abdominal pain one month after infection. Developed bilateral pleural effusion with high eosinophilic count both in pleural effusion and in peripheral blood three months after infection. Ova first found one year later with cystic nodular shadows in the lungs. Changeable degree of perifocal infiltrations. Decreased eosinophilic count in peripheral blood later.

Case 3: W. T. J. 21 year old man. Kiangsunese. Son of Case 2.

Crabs eaten: Only once in October 1953 with Case 2.

First clinical symptoms: Epigastric pain and chest pain in early December 1953. Cough in late December 1953. Blood-streaked sputum in April 1954.

Clinico-roentgenological follow-up: December 12, 1953—Bilateral pleural reaction with a tiny increased density in right upper lung (Fig. 3A). White blood cells 39,300, Eosinophil 0 per cent, Ova (—) in sputum. January 5, 1954—Bronchopneumonic lesions in both lower lung fields (Fig. 3B). White blood cells 29,500, Eosinophil 1 per cent, Ova (—) in sputum. February 19, 1954—Bronchopneumonic lesions disappeared. Left pleural reaction present. White blood cells 28,000, Eosinophil 1 per cent, Ova (—) in sputum. April 29, 1954—Soft hazy densities in left upper, middle and both lower lungs. White blood cells 18,500, Eosinophil 55 per cent, blood-streaked sputum (+) but Ova (—) in sputum. July 13, 1954—Pericardial effusion with soft densities in right middle and lower lung fields. White blood cells 19,500, Eosinophil 61 per cent, Tubercle bacilli (—) and Ova (—) in sputum. Subcutaneous creeping tumor (+). July 28, 1954—Pericardial effusion. Soft infiltration in left upper and right middle lung fields (Fig. 3C). White blood cells 17,100, Eosinophil 61 per cent, Tubercle bacilli (—) and Ova (—) in sputum. Pericardial effusion, transparent, Eosinophil (—). February 3, 1956—Cystic nodules in right upper and left middle lung fields and ill-defined patch in right middle lung fields (Fig. 3D). Ova first found in sputum. September 7, 1956—Ill-defined patch in the right middle lung field disappeared. More cystic nodules in the right lower lung. Ova (+) in sputum. May 31, 1957—Fibrotic lesion in right upper lung field. Cystic nodular lesions in right lower and left middle lung fields (Fig. 3E). White blood cells 5,200, Eosinophil 7 per cent, Ova (+) and Tubercle bacilli (—) in sputum. April 18, 1958—More cystic nodular shadows in right lower and left middle lung fields. White blood cells 8,850, Eosinophil 10 per cent, Ova (+) in sputum.

Treatment: Several courses of emetine injection.

Result: No cure.

Comment: Began with epigastric and chest pain, laminary pleurisy and intrapulmonary soft infiltration one and a half months after injection. Transient bronchopneumonic or soft pneumonic infiltrations with marked leucocytosis and high eosinophilic count for more than half a year without final isolations of ova. Pericardial effusion and subcutaneous creeping tumor developed nine months after infection. Cystic nodular shadows with variable degree of perifocal infiltrations became apparent later with parasite ova found in bloody sputum.

Case 4: C. I. F. 40 year old man. Chekiangnese. Father of Case 5.

Crabs eaten: Once in early 1954.

First clinical symptoms: Chest pain and cough in May 1954. Recurrent bloody sputum since summer 1954.

Clinico-roentgenological follow-up: May 3, 1954—Right side pleural effusion. White blood cells 10,500, Eosinophil 40 per cent, Ova (—) and Tubercle bacilli (—) in sputum. Pleural effusion yellowish transparent. Ova first proved in sputum since summer 1954. October 12, 1954—Right pleurisy disappeared. Soft infiltration in the right middle lung field. Ova (+) in sputum. January 14, 1955—Pleurisy reappeared in right chest. Infiltrative shadow in right middle lung field absorbed with small nodules remained. February 28, 1955—Right pleural effusion increasing in amount. Linear shadow in right lower lung field. March 29, 1955—Pleural effusion slightly decreased. June 2, 1955—As before with pleural effusion. July 11, 1955—As before with pleural effusion. August 30, 1955—As before with pleural effusion. February 7, 1956—Soft infiltration in right middle and lower lung fields. Pleurisy is the same (Fig. 4A). March 18, 1956—Right pleurisy and pulmonary infiltration are both increasing. April 6, 1956—Both pleural effusion and pulmonary infiltration markedly decreased with cystic nodular shadow remained in the right middle lobe anteriorly (Fig. 4B). White blood cells 7,800, Eosinophil 10 per cent, Ova (+) in sputum. June 19, 1957—Fibrotic lesion in right lower lung. Cystic nodule disappeared (Fig. 4C). White blood cells 6,200, Eosinophil 4 per cent, Ova (—) in sputum. May 1, 1958—As before. White blood cells 7,500, Eosinophil 2 per cent, Ova (—) in sputum.

Treatment: Emetine injection every year since 1954 to 1956.

Result: No symptom since winter 1956.

Comment: Began with pleurisy, leukocytosis and high eosinophilic count two to three months after infection. Ova first found another two to three months thereafter. Cystic nodule with varying degree of perifocal infiltration. Pleural effusion developed again (late pleurisy) with turbid effusion which lasted one and a half years. Normal white blood cells and eosinophilic count in later stage. Fibrotic lesion remained after cure.

Case 5: C. H. H. 15 year old girl. Chekiangnese. Daughter of Case 4.

Crabs eaten: Once in early 1954 with her family.

First clinical symptoms: Substernal discomfort, abdominal pain and neck swelling in mid April 1954.

Clinico-roentgenological follow-up: April 27, 1954—Bilateral laminary pleurisy. White blood cells 22,200, Eosinophil 63.5 per cent, Ova (—) and Tubercle bacilli (—) in sputum. Ova first found in autum 1954. April 10, 1957—Typical cystic nodular pattern in left upper lung field (Fig. 5A). Complained of hemoptysis. White blood cells 7,200, Eosinophil 20 per cent, Ova (+) and Tubercle bacilli (—) in sputum. April 17, 1957—Tomogram shows cystic nodules in left upper lung field (Fig. 5B). May 11, 1957—Lesions in left upper lung field seems more confluent. April 23, 1958—Lesions in left upper lung field become fibrotic and partially cystic. White blood cells 10,900, Eosinophil 1 per cent, Ova (—) in sputum.

Treatment: Emetine injection since 1954 totally about 100 ampules (40 mg.).

Result: Relatively good response to emetine treatment.

Comment: Began with chief complaints of substernal discomfort, abdominal pain, laminary pleurisy with marked leukocytosis and high eosinophilic count 2 months after infection. Ova first found half a year after infection. Typical cystic nodular pattern on chest x-ray films later on which became fibrotic recently. Eosinophilic count decreased in later stage.

SUMMARY

1. On the basis of clinical observations of more than 300 cases of pulmonary paragonimiasis since 1948, of which some 40 cases are followed up for more than 3 years up to 10 years, we think, in order to understand the entire clinical course of lung fluke disease, it is reasonable and advisable to divide into three stages as follows: 1. stage of migrating larvae; 2. stage of mature worms, and 3. stage of recovery.

2. The clinical manifestations of the first stage which may develop one month longer after infection, are pleurisy with or without effusion, often bilateral, seropneumothorax, transient pneumonic or bronchopneumonic infiltrations, pericarditis, subcutaneous creeping tumors and other extrapulmonary infestations having clinical symptoms of abdominal pain, chest pain, cough, blood streaked sputum and general malaise. The first stage lasts 3 months to almost one year or even more.

3. The main clinical feature of the second stage is recurrent bloody, characteristically chocolate-colored sputum with ova in the sputum and nodular or cystic nodular

shadows with changeable degree of perifocal infiltrations demonstrated in serial chest x-ray films. Secondary pleurisy, often encapsulated and with turbid effusion, or pyopneumothorax may be noted at this stage. The duration of the second stage is quite variable, partly depends on the efficacy of the treatment.

4. At the third stage, all clinical symptoms and signs disappear with resultant complete disappearance of abnormal chest x-ray findings seen during the second stage. Residual hard nodule or even calcified spot as well as fibrotic lesions may remain.

5. In the present paper, the entire clinical features of each stage have been discussed in detail including symptoms and signs, serial chest x-ray findings, laboratory data, diagnostic as well as differential diagnostic clues of lung fluke disease. Extrapulmonary manifestation and treatment are mentioned briefly.

RESUMEN

1. Basándose en la observación clínica de más de 300 casos de paragonimiasis desde 1948, de las que alrededor de 40 se observaron por más de tres años y hasta 10 años, pensamos que a fin de comprender la enfermedad, es conveniente dividirla entre períodos: 1. Período de la migración de las larvas; 2. Período de maduración del gusano; 3. Etapa de recuperación.

2. Las manifestationes clínicas del primer período que habitualmente se presentan a partir de un mes cuando menos, pero generalmente más tarde, después de la infección, son: pleuresía, menudo bilateral, con ó sin derrame, sero-neumotórax, infiltraciones transitorias neumónicas o bronconeumónicas, pericarditis, tumores subcutáneos emigrantes y otras infestaciones extrapulmonares, con síntomas de dolor abdominal, dolor torácico, tos, esputos estriados de sangre, y malestar general. Este primer período dura de tres meses a casi un año.

3. Las características principales del segundo período, son: esputo sanguinolente recurrente, de color achocolatado característico, con huevecillos en él, y en la radiografía, se observan manchas nodulares o quísticas con grado variable de infiltración perifocal según se ve en las series de películas. La pleuresía secundaria a menudo encapsulada y con derrame turbio o pio-neumotórax, pueden observarse en esta etapa. La duración de ésta es muy variable y depende de la eficacia del tratamiento.

4. En el tercer período todos los signos clínicos desaparecen, con una desaparición de los aspectos radiológicos también. Pueden queder nódulos duros residuales o aún puntos calcificados, así como lesiones fibrosas.

5. En este trabajo se discute el cuadro clínico de cada etapa, incluyendo el aspecto clínico, el radiológico, datos de laboratorio así como las bases para el diagnóstico diferencial de esa enfermedad. Se mencionan brevemente las manifestaciones extrapulmonares así como el tratamiento.

RESUME

1. Sur la base d'observations cliniques portant sur plus de 300 cas de distomatose pulmonaire depuis 1948, parmi lesquelles quelque 40 cas ont été contrôlés pendant plus de 3 ans, et jusqu'à 10 ans, l'auteur pense que, pour comprendre l'évolution clinique complète de l'atteinte pulmonaire, il est raisonnable et souhaitable de la diviser en trois phases: 1. phase des larves migratrices; 2. phase des vers arrivés à maturité; 3. phase de guérison.

2. Les manifestations cliniques de la première phase peuvent se développer un mois après l'infection, parfois moins mais généralement davantage. Ce sont la pleurésie, souvent bilatérale avec ou sans épanchement, le séropneumothorax, les infiltrations pneumoniques ou bronchopneumoniques transitoires, la péricardite, les tumeurs sous-cutanées et d'autres localisations extra-pulmonaires qui donnent des symptômes de douleur abdominale, thoracique, de la toux, des expectorations teintées de sang, et un malaise général. Le premier stade dure de trois mois jusqu'à presque une année.

3. La principale caractéristique clinique du second stade est l'expectoration sanglante récidivante, caractérisée par sa couleur chocolat, contenant des oeufs, et l'existence d'ombres nodulaires ou nodulo-kystiques, avec un degré variable d'infiltrations autour du foyer principal mises en évidence par les clichés en série. Une pleurésie secondaire, souvent enkystée, avec épanchement trouble, ou un pneumothorax, peuvent être notés à ce stade. La longueur de cette seconde phase est assez variable, et dépend pour une part de l'efficacité du traitement.

4. Au troisième stade, tous les symptômes cliniques et les manifestations cessent avec disparition complète consécutive des constatations radiologiques anormales vues lors du deuxième stade. Un nodule résiduel, ou souvent une calcification, ainsi que des lésions fibreuses peuvent persister.

5. Dans le présent article, les caractéristiques cliniques complètes de chaque stade ont été discutées en détail, y compris les symptômes et les signes, les constatations radiologiques en série, les données de laboratoire, le diagnostic, ainsi que le diagnostic différentiel de la distomatose pulmonaire. La manifestation extrapulmonaire et le traitement sont brièvement mentionnés.

ZUSAMMENFASSUNG

1. Wir halten es auf der Grundlage der klinischen Beobachtungen an mehr als 300 Fällen von Lungen Paragonimiasis seit 1948, von denen mehr als 40 Fälle mehr als drei Jahre und bis zu 10 Jahren nachbeobachtet wurden, für empfehlenswert, um den gesamten klinischen Ablauf der Lungenegelkrankung zu verstehen, eine Einteilung in drei Stadien wie folgt vorzunehmen: 1. Stadium der wandernden Larven; 2. Stadium der reifen Würmer; 3. Stadium der Erholung.

2. Im ersten Stadium, das sich frühestens einen Monat, aber für gewöhnlich länger nach der Infektion entwickeln kann, bestehen die klinischen Manifestationen in Pleuritis, oft bilateral mit oder ohne Erguss, Seropneumothorax, vorübergehende pneumonische oder bronchopneumonische Infiltrationen, Pericarditis, subkutan wachsende Tumoren und andere extrapulmonale Absiedlungen, deren klinischen Symptome in Leibschmerz, Brustschmerz, Husten, blutigverfärbten Sputum und allgemeinem Unwohlsein bestehen. Das erste Stadium dauert 3 Monate bis 1 Jahr.

3. Die wesentlichen klinischen Merkmale des zweiten Stadiums sind wiederkehrendes, blutiges, charakteristisch schokoladenfarbiges Sputum mit Eiern im Sputum und Knoten oder cystisch-knotigen Schatten mit wechselnden Graden von perivokalen Infiltrationen, nachweisbar an Röntgenbildreihen. Sekundäre Pleuritiden, oft abgekapselt und mit getrübten Erguss oder Pyopneumothorax können in diesem Stadium beobachtet werden. Die Dauer des 2. Stadiums ist ganz verschieden und hängt zum Teil von der Wirksamkeit der Behandlung ab.

4. Im dritten Stadium verschwinden alle klinischen Symptome und zeigen mit entsprechend vollständigem Verschwinden pathologischer Thoraxröntgenbefunde, die während des zweiten Stadiums zu sehen waren. Es können restliche verhärtete Knoten oder auch Kalkschatten ebenso wie fibrotische Herde zurück bleiben.

5. In der vorliegenden Mitteilung wurden sämtliche klinischen Eigenheiten eines jeden Stadiums im Detail besprochen einschliesslich Symptome und Anzeichen, Röntgenbildreihen, Laborwerte und diagnostischen ebenso wie differentialdiagnostischen Anhaltspunkten der Lungenegelerkrankungen. Extrapulmonale Manifestationen und Behandlung werden kurz gestreift.

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Corticosteroids in Human Tuberculosis*

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A year ago[1] we presented to the Argentine Society of Tuberculosis our first cases of patients suffering from tuberculosis to whom cortisone or some of its derivatives had been administered in addition to modern medical treatment.

Eight patients had been given the drug in 1955 or at the beginning of 1956, and their evolution has been followed by us up to the present (April 1958). Based on that first experience and informed by the abundant bibliography published on this subject, we have continued supplying corticosteroids to certain types of patients suffering from tuberculosis.

All this has allowed us to establish more and more precisely, the indications to follow for this complementary treatment of tuberculosis. We have never observed disorders attributable to the administration of cortisone in our patients, and the principle we follow to establish the strict indications is based on the positive information of immediate subjective clinical improvement. The later evolution of tuberculous lesions has continued as in any other patient, a logical thing when considering that *the corticosteroids do not act either upon the specific lesion or the Koch bacillus.* Its action is mainly antiexudative, anti-inflammatory, nonspecific and of immediate action. Acting upon the nonspecific alterations of the tuberculous patient, it contributes not only to the quick recovery of his general condition but it also favors the action of antituberculosis drugs on bacilli.[2] Due to the reasons already mentioned we also believe that there is no object in considering the late results of the application of cortisone to the patients with tuberculosis. The first of them were treated with cortisone; but since the introduction of the prednisone we only employ this hormone, whose advantages over the above mentioned are well known.

Requirements to be fulfilled for the employment of corticosteroids in tuberculosis

A number of conditions must be fulfilled when drugs of the cortisonic type are administered to a tuberculous patient. They cannot be forgotten for the consequences could become disastrous.

1. Treatment with antituberculosis drugs: The patient to whom an hormone like prednisone is administered must always be under treatment with tuberculoustatics; these will continue to be administered a long time after the hormone has been withdrawn.

2. Use of Isoniazid: This is the most powerful antituberculosis drug available; therefore, with the exception of some special situation that must always be included in treatment. Moreover, it seems to have been demonstrated that the isoniazid potentializes the action of cortisone when inhibiting its destruction at the level of the liver.[3,4] Thus, the use of both

*This work has been carried out in Ward V of the Muñiz Hospital, Buenos Aires, and presented before the Argentine Chapter, American College of Chest Physicians, Concordia, November 10, 1957.

substances would make the attainment of the same results with smaller quantities of prednisone possible.

3. Study of sensitivity of the Koch bacillus to antituberculosis drugs: It is an essential requirement, when using prednisone, that the patient be protected by effective antituberculosis drugs, that is to say, that there must not exist any grade of resistance to isoniazid or streptomycin. If the patient has never received antituberculosis drugs, it can usually be assumed in practice, that his bacilli are sensitive to the drugs, but if he has already received them for several months, it is imperative to determine whether the organisms have become resistant. A patient whose bacilli are resistant to isoniazid or streptomycin, when receiving hormonal treatment, runs the risk of becoming worse instead of improving. This accounts for some unfavorable results reported in certain patients during hormone therapy.[5] If bacilli are resistant to some of the drugs, the situation is similar to that of the tuberculous patient who only receives cortisone. When there is an urgent indication to administer hormonal treatment (meningitis, etc.) and the patient has not previously received isoniazid or streptomycin, one is justified in proceeding without this investigation.

4. Knowledge of the disadvantages of hormone therapy: Even if hormone therapy is employed in tuberculous patients in small quantities and for short periods, the doctor must not ignore the disturbances that may appear in certain cases. A syndrome of hypercortisonism (in which excessive appetite, euphory, insomnia, nervous excitement, retention of fluids, edema, irregular menstruation, acne and many other symptoms occur) has been described; one must be attentive to any manifestation of symptoms so as to take the appropriate measures.

5. Glycemia must be normal: This fact must be observed because of the tendency to hyperglycemia of the corticosteroids.

6. Use of prednisone or prednisolone: Is reported to have great advantage over cortisone, especially because of its action in the retention of fluids and the production of edemas.

Risks in the use of corticosteroids in tuberculous patient

1. Patients suffering from tuberculosis to whom cortisone, its derivatives or ACTH are given without being protected simultaneously by drugs (such as isoniazid, streptomycin, aminosalicilic acid) always show advance of their lesions. Thus the employment of those hormones was contraindicated for a time. Once this relation and the form of avoiding its disastrous action were known, hormone therapy was incorporated in the bacilli arsenal.

2. Cortisone and its derivatives make the cicatrization of any inflammatory lesion difficult, and therefore, it can delay sclerosis and retraction of the cavitary lesions. In those patients having old caverns, not completely stabilized, without an exudative component, hormone therapy may be unfavorable. In certain cases it stops the curative process, giving what Brocard has called the "cavitary inertia".[2]

3. Action of cortisone in culture of bacteria. In solid mediums the addition of cortisone helps the growth of colonies of bacilli. If streptomycin

is added to this solid medium, the presence of cortisone partly inhibits the action of the antibiotic, facilitating also the bacillar development.[8]

Indications of the hormone therapy in tuberculosis

Notwithstanding the bad effect that cortisone or ACTH had on the reactivation of tuberculous lesions when they were employed in the treatment of rheumatic or other processes;

Notwithstanding the evident anticicatricial effect that these drugs have restraining the proliferation of the fibrous tissue;

In spite of the evidences obtained "in vitro" demonstrating the favorable action that these hormones have on the growth of bacilli;

The experience of these last years has rendered us the possibility of establishing the indications of this therapy in tuberculosis. It has been employed in many patients, in all clinical forms, in different localizations and it is on this basis that we are able to gather the useful indications. Being powerful and at the same time riskful for the patient, it is necessary to follow the fixed patterns strictly, to know the danger that its employment can cause and to fulfill all the requisites we have mentioned before.

Useful indications

a) *Pulmonary tuberculosis:*
   1. The presence of exudative lesions, in any period of tuberculosis (primary, extraprimary).
   2. When tuberculosis alters in a great measure the general state of a patient (miliary forms).
   3. The evolutive outbreaks during the course of a chronic sickness.
   4. The addition of tuberculosis to another illness that requires the hormone therapy (asthma, rheumatoid arthritis, Addison's illness).
   5. In post-operative stages of severe tuberculosis, when shock occurs (according to different authors, cortisone or ACTH may be used).
   6. When acute or serious laryngeal and bronchial lesions are added to the pulmonary localization.

Hormones must not be employed in patients suffering from chronic cavitary tuberculosis.[2, 11]

b) *Tuberculosis of the serosa* (pleura, pericardium, polyserositis). There is a tendency of employing cortisone frequently, especially in severe cases. It would favour the reabsorption of the exudation and it would also produce an antiadhesive action.

Dose

Since the advent of prednisone we employ only this drug, thus replacing cortisone which was used at first.

We administer 20 milligrams on the first day and 10 milligrams a day in two doses thereafter.

When the patient suffers only from tuberculosis, we administer the hormones during four or six weeks. The treatment is prolonged when another sickness requiring it coexists.

We have not used ACTH at the end of the cortisonic treatment because we do not believe it is necessary.

No inconveniences have occurred when using these drugs.

Our patients

We report our experience with 30 patients suffering from tuberculosis who have been treated with corticosteroids (Figs. 1, 2 and 3). With the exception of the first patients, who were given cortisone, the majority were treated with prednisone.

They presented serious cases of post-primary pulmonary tuberculosis, with notable alteration of the general condition; some of them presented outbreaks that receded without difficulty with the cortisonic medication.

A young woman who suffered both from tuberculosis and Addison's disease, recovered from the tuberculosis, and in spite of having been given prednisone subsequently on several occasions for Addison's disease, she has not suffered from any pulmonary alteration. Five had ulcerated laryngeal lesions, which responded well in a short time. One with unilateral serofibrinous pleurisy, improved rapidly.

Considerations

It is our belief that the last word on corticosteroids and tuberculosis has not yet been said. Therefore, many of those who were opposed to the use of these drugs for a number of years, now admit their extraordinary and unquestionable benefit on grave cases of tuberculosis.[12]

Other authors, especially in France, have been employing this medication for several years and are strong supporters of it.

In our group of patients (many of them have been treated for two years) we have observed surprising improvements.

The worse the patient is, the quicker and more certain his recovery will be, especially if he has not previously had antituberculosis drugs.

Following the strict rules we have already established and applying the corticosteroids to those who present good indications, much benefit is observed in the course of the disease.

SUMMARY

Cortisone and ACTH were contraindicated for patients suffering from tuberculosis up to 1952. Since that date, opinions gradually evolved, as it was seen that these hormones did not aggravate tuberculous lesions provided specific drugs (streptomycin, isoniazid, PAS) were administered simultaneously.

Later it was demonstrated that both cortisone and ACTH or their derivatives are helpful in the treatment of severe forms of tuberculosis.

In this paper, requirements and dangers for its employment, as soon as its proper indications are considered.

Thirty patients have been treated successfully with cortisone.

RESUMEN

La cortisona y sus derivados estuvieron contraindicados en aquellos enfermos portadores de una tuberculosis hasta 1952. A partir de entonces los conceptos fueron cambiando, pues se vió que estas hormonas no agravaban las lesiones tuberculosas si, simultáneamente se suministraban medicaciones específicas (estreptomicina, PAS, isonizida).

En una tercera etapa se ha demostrado que, tanto la cortisona como la ACTH o sus derivados son una ayuda de gran importancia para el tratamiento de las formas graves de la tuberculosis.

Se exponen en esta comunicación las indicaciones de esta terapéutica hormonal en tisiología, y se presentan 30 casos tratados con éxito con esta asociación.

RESUME

La cortisone et l'ACTH étaient contre-indiquées pour les malades atteints de tuberculose jusqu'en 1952. Depuis cette date, les opinions ont progressivement évolué, et

We are grateful to Lepetit Laboratories for having made this study possible.

on a constaté que ces hormones n'aggravaient pas les lésions tuberculeuses, pourvu que des médications spécifiques (streptomycine, isoniazide, P.A.S.) fussent administrées en même temps.

Plus tard, il fut démontré que les deux médications, cortisone et ACTH ou leurs dérivés, sont utiles dans le traitement des formes graves de tuberculose.

Dans cet article, les nécessités et les dangers de son utilisation, aussi bien que ses indications propres sont analysées.

30 malades ont été traités avec succès par la cortisone.

ZUSAMMENFASSUNG

Bis zum Jahre 1952 waren Cortison und ACTH kontraindiziert für mit Tuberkulose behaftete Kranke. Seit diesem Zeitpunkt entwickelten sich allmählich andere Anschauungen, nach dem sich herausgestellt hatte, dass diese Hormone tuberkulöse Herde nicht verschlechterten, vorausgesetzt, dass gleichzeitig eine spezifische Therapie (Streptomycin, PAS, INH) gegeben wurde.

Später konnte nachgewiesen werden, dass sowohl Cortison als auch ACTH oder Derivate von Nutzen waren zur Behandlung schwerer Formen von Tuberkulose. In dieser Mitteilung werden die Erfordernisse und Gefahren für ihre Anwendung betrachtet und ebenso ihre genaue Indikation.

30 Patienten wurden erfolgreich mit Cortison behandelt.

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The Incidence, Distribution and Morphology of Lymphadenogenous Perforative Bronchial Scars in Adults

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The interest which is shown in the more recent European literature in perforative bronchial lesions is mainly the result of two factors: the more frequent application of radiologic[1, 2] bronchoscopic [1-3] and bronchographic[4] technics in the evaluation of bronchial lesions, and the increased emphasis on the importance of the lymphatic system in the pathogenesis of pulmonary tuberculosis. The latter factor is further brought into prominence by the relative resistance of tuberculous lymph nodes to the effect of modern antituberculosis therapy.[2, 5] Over 1,000 references on perforations of tuberculous lymph nodes into the bronchial tree are now available.[6]

Fresh lymphadenogenous bronchial perforations result in characteristic, localized, circumscribed bronchial lesions which differ morphologically and pathogenetically from the caseous, ulcerative bronchial lesions which originate from implantation and spread of tuberculous infection by continuity.[7] They can be observed in all the phases of pulmonary tuberculosis.[1, 8-10] Although a large percentage of them heal without sequelae,[11] localized residual scars at typical sites frequently remain and can often be detected many years later at autopsy.

The relative scarcity of reports on perforative bronchial lesions in the American literature suggested the possibility that perforative bronchial lesions and scars might be less common in the United States than in Europe. Hence the following study.

Materials and Methods

The study is based on material which came to routine autopsy between 1953 and 1955 at a hospital for patients with mental disease, the Warren State Hospital, Pennsylvania. There were 197 available autopsies during these years, all of which were performed by the Chief Pathologist, Dr. P. Schwartz.

After removing the lungs and the tracheobronchial lymph nodes in toto, the bronchi were opened through their dorsal walls and examined macroscopically for the presence of perforative bronchial lesions and scars. Specimens with positive findings were nailed to a wooden block so as to display the opened bronchial tree and preserved in 10 per cent solution of formalin.

Findings

1. Incidence and distribution:

In the 197 autopsies, 54 (27.4 per cent) cases showed perforative bronchial lesions and scars in the lungs. Twenty-nine were men and 25 women.

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Their ages ranged from 24 to 92, and from 39 to 86 years respectively. Seventy-eight per cent of both men and women were over the age of 60.

In 41 of the 54 cases, the lesions were confined to the bronchi of a single lung: in 25 to the right and in 16 to the left lung. The remaining 13 showed multiple, bilateral bronchial lesions.

The distribution of the total of 92 perforative bronchial lesions and scars is shown in Figure 1.

2. Morphology:

The bronchial scars were classified according to their appearance in the following order of frequency:

1. Circular, flat scars	24
2. Circular, depressed	24
3. Trough-shaped	13
4. Diverticular	11
5. Long, suture-like	11
6. Pinhead sized and star-shaped	8
7. Funnel-shaped	5

Figures 2, 3 and 4 illustrate examples of circular-flat, circular-depressed, and diverticular scars respectively: they were present in identical sites in the right lower lobe bronchus, and show increasing degrees of depth of the lesions. The diverticular scar (Figure 4) closely resembles in appearance a bronchial orifice, for which it might well be mistaken on bronchoscopy.

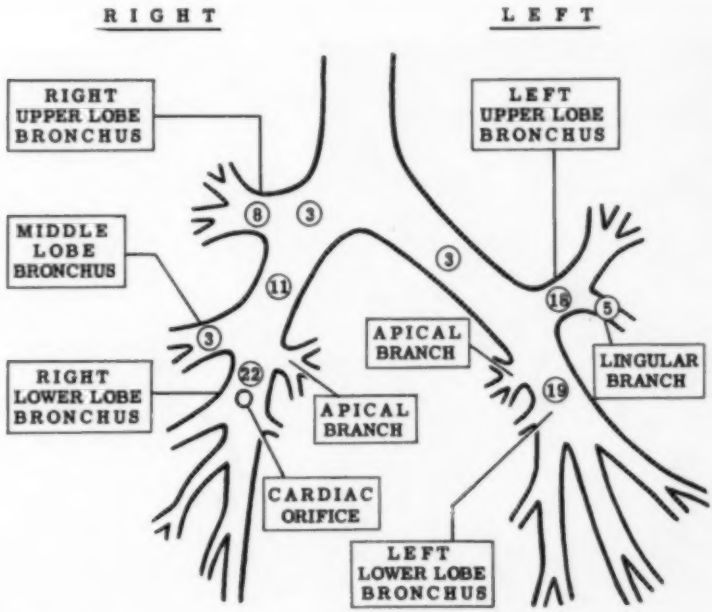

FIGURE 1: Frequency and distribution of perforative lesions and scars in the bronchial tree.

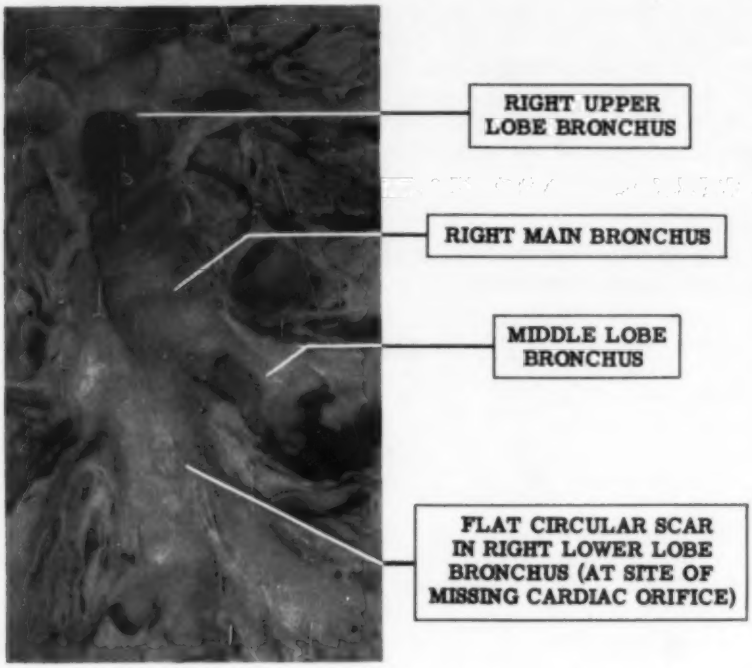

FIGURE 2: Flat circular scar in the right lower lobe bronchus.

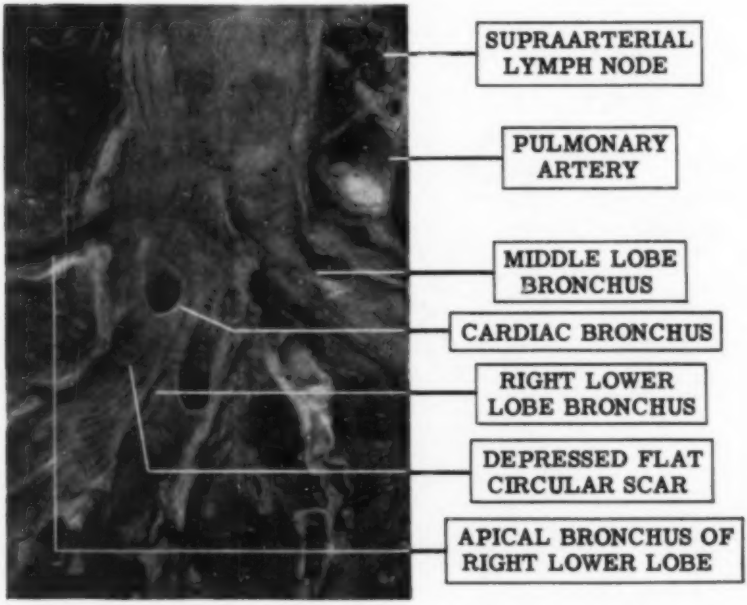

FIGURE 3: Depressed, flat circular scar in right lower lobe bronchus.

3. Association of bronchial scars with calcified hilar lymph nodes, gross distortion of the major bronchi, and lobar atelectasis:

Radiographs of removed lungs offer a useful technique for investigation of the relationship between bronchial scars and calcified hilar lymph nodes. For technical reasons, this approach could not be carried out at the time the material was under study. The findings reported here are therefore limited to gross macroscopical examinations of the specimen.

Calcified paratrachial, hilar and parabronchial lymph nodes were present on the same side as the scar in 31 cases. In 19, the calcified lymph node was either attached to the scar or in its immediate proximity.

In eight cases, the local damage to the bronchus resulted in a definite palpable loss of bronchial cartilage. Some distortion of the bronchus at the site of the lesion was present in the majority of the autopsies although its degree and extent was difficult to evaluate without previous bronchograms. In seven cases, however, stenosis of the bronchus was most marked, and in four of which the lobe supplied by the stenosed bronchus was found to be atelectatic and fibrosed: twice the middle lobe, and once each the right upper lobe and the lingula.

Figures 5A and 5B illustrate the association between a perforative bronchial scar, calcified hilar lymph nodes and lobar atelectasis. The superior interlobar space of the right lung is seen to be greatly contracted. The main stem of the right pulmonary artery is a strikingly narrow tube surrounded by calcified hilar lymph nodes. The main bronchus of the middle lobe is similarly narrowed, with calcified lymph nodes in immediate proximity. A trough-shaped, bronchial scar 15 mm. long is seen obliquely to extend from the middle lobe orifice towards the carina. The bronchial wall

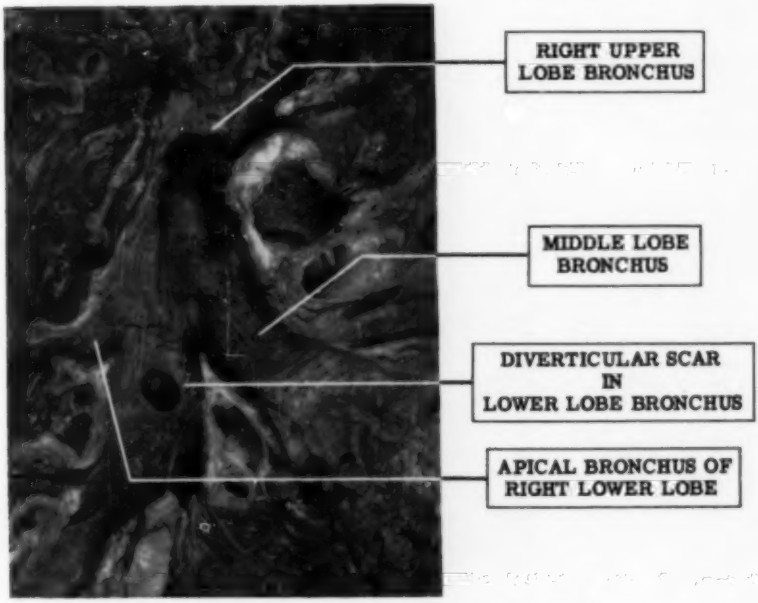

FIGURE 4: Diverticular scar in right lower lobe bronchus.

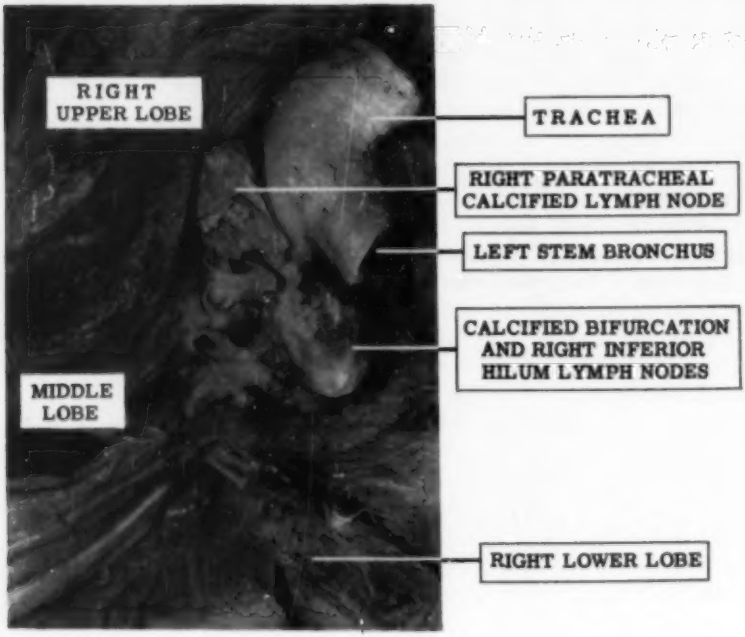

FIGURE 5A: Association between a perforative bronchial scar, calcified hilar lymph nodes and lobar atelectasis: hilar aspect.

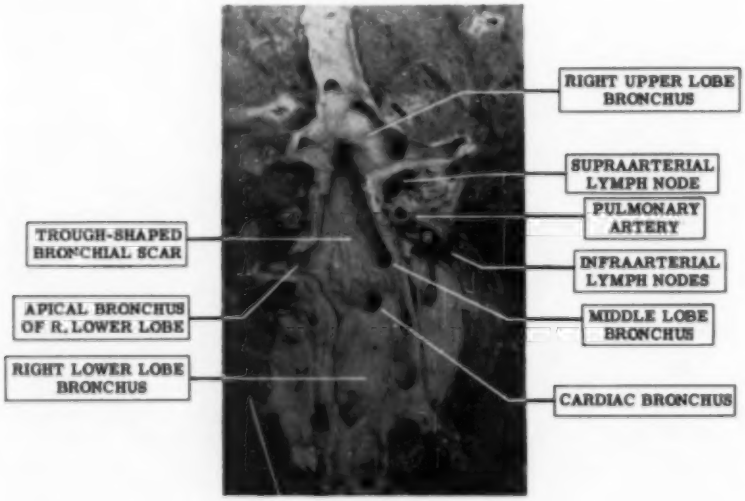

FIGURE 5B: Association between a perforative bronchial scar, calcified hilar lymph nodes and lobar atelectasis: bronchial aspect.

is distorted, the lumen narrowed, and the middle lobe distal to it airless, fibrotic and contracted.

The large calcified lymph node complex which produced the perforative bronchial lesion and scar is seen from the hilar aspect (Figure 5A) to be a conglomeration of bifurcation lymph nodes, inferior hilum angle lymph nodes, and lymph nodes of the anterior wall of the proximal part of the middle lobe bronchus.

In another example in this series, published as a separate case study, an even more striking bronchial defect due to a perforative bronchial scar was found: the perforative bronchial lesion on the right upper lobe bronchus produced a complete bronchial amputation, with resulting separation, atelectasis, fibrosis, and shrinkage of the right upper lobe.

DISCUSSION

The literature on perforative bronchial lesions and scars has been reviewed in a number of fairly recent publications.[6, 8, 10, 12, 14] The reported incidence of such lesions reflects disagreement with regard to the incidence of tracheobronchial tuberculosis generally: among tuberculous patients this is estimated to vary from 10 per cent to 66 per cent on bronchoscopy and from 3 per cent to 90 per cent at autopsy.[16]

The incidence of perforative bronchial lesions in primary tuberculosis is generally stated to vary between 10 and 60 per cent,[8, 12, 13] with a conservative estimate of between 10 and 20 per cent.[9] Here racial and regional differences in susceptibility to severe lymphadenogenous reactions may be an important factor.[12] A similar range of incidence, however, is observed by different workers also in postprimary tuberculosis. The highest reported frequency of perforative bronchial lesions and scars as detected at autopsy on tuberculous subjects of all ages is 90 per cent.[16]

Among routine autopsies on the general population at least three independent European centers report an incidence of perforative lesions and scars in over 20 per cent of the cases.[15-18] The evidence for considering these bronchial scars to be the result of perforative lesions is discussed by Wyss.[18] In this series the criteria for considering the bronchial scars to be of perforative origin rests largely in their typical appearance as described in publications referred to in this paper, their characteristic location, and the presence of calcified lymph nodes in close proximity in 35 per cent of the cases. Using radiographs of removed lungs, Wyss[18] found calcified lymph nodes in close proximity to 66.1 per cent of the scars. Voegtli[17] attributes a tuberculous origin to 77.9 per cent of the scars in his series of routine autopsy material.

Most authors agree that perforative bronchial lesions occur more often on the right side than on the left, although their ratios vary widely on different estimations.[18] The preponderance of right sided scars is influenced by the anatomy of the lymphatic drainage of the lungs. Lung fields on the left side often drain directly into the lymph nodes situated on the right side, while the lymphatic drainage of the right side is almost exclusively confined to lymph nodes on that side.[1, 16]

The morphology of perforative bronchial lesions and scars is influenced by their age, size and location. Since perforative bronchial lesions heal rapidly, it is not surprising that examinations undertaken at different stages of the perforative defect should produce widely different findings. Also, it has been estimated that only about 50 per cent of the perforative bronchial lesions are accessible to bronchoscopic examination.[11] A large number are found not to be associated with any marked clinical symptoms or radiologic findings and are thus discovered by chance on routine examination. The more serious sequelae include bronchiectasis, and bronchial stenosis of varying degrees of severity: the latter impair drainage and cause disturbances in pulmonary ventilation. In extreme instances, they are associated with lobar atelectasis and fibrosis. A possible causative relationship between bronchial scars and the development of bronchial carcinoma has been suggested, but not satisfactorily established.[12, 17]

SUMMARY

The relative scarcity of reports on perforative bronchial lesions and scars in the American literature suggested the possibility that such lesions and scars might be less common in the United States than in Europe. A study of the bronchial trees of 197 routine autopsy specimens showed the presence of typical perforative bronchial lesions and scars in 54 (27.4 per cent), an incidence which is comparable to the results obtained by workers in Europe. In 25 cases, the lesions were confined to the bronchi of the right lung; in 16 cases, to the bronchi of the left lung. The remaining 13 cases showed multiple, bilateral bronchial lesions. The lesions are believed to originate in perforations of tuberculous lymph nodes into the bronchial tree.

Acknowledgment: The author wishes to acknowledge the kind guidance of Profes-

sor P. Schwartz. It is with his permission that this material is presented. Kirsten Grosz provided valuable technical assistance.

RESUME

La rareté relative des fistules bronchiques et des cicatrices de perforations bronchiques relevées dans la littérature américaine ont amené à penser que de telles lésions et cicatrices seraient moins communes aux Etats-Unis qu'en Europe. Une étude de l'appareil bronchique de 197 autopsies courantes montra la présence de lésions bronchiques perforatives typiques, et de leurs cicatrices dans 54 cas (27,4%), fréquence qui est comparable aux résultats obtenus par les chercheurs en Europe. Dans 25 cas, les lésions étaient limitées aux bronches du poumon droit; dans 16 cas, aux bronches du poumon gauche. Les 13 autres cas montrèrent des lésions bronchiques multiples, bilalésions étaient limitées aux bronches du poumon droit; dans 16 cas, aux bronches du tuberculeux dans l'arbre bronchique.

ZUSAMMENFASSUNG

Die relative Spärlichkeit von Berichten über perforierende Bronchialveränderungen und Narben in der amerikanischen Literatur lassen die Möglichkeit vermuten, dass solche Veränderungen und Narben in den Vereinigten Staaten weniger häufig sind als in Europa. Eine Untersuchung der Bronchialbäume bei 197 routinemässig gewonnenen Sektionspräperaten ergab das Vorliegen von typischen perforierenden Bronchialveränderungen und Narben in 54 Fällen (27,4%), ein Vorkommen, das dem von anderen Untersuchern in Europa gewonnenen Ergebnissen vergleichbar ist. In 25 Fällen waren die Veränderungen auf die Bronchien der rechten Lunge beschränkt, in 16 Fällen auf die Bronchien der linken Lunge. Die restlichen 13 Fälle zeigten multiple, bialterale bronchiale Veränderungen. Es wird angenommen, dass diese Veränderungen von Perforationen tuberkulöser Lymphknoten in den Bronchialbaum stammen.

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SECTION ON CARDIOVASCULAR DISEASES

The Electrocardiogram in Atrial Septal Defect*

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In an effort to determine the mechanism of the predominant pattern in the electrocardiogram in atrial septal defect we have studied tracings of a number of individuals whose condition was treated by surgery. The patient group presented two obvious advantages: 1) in each case the lesion had been anatomically defined, and 2) comparison could be made in the survivors of tracings before and after repair.

Material

Seventy-nine consecutive patients in whom atrioseptopexy[1] was performed were considered. The age range was two to 57 years, the majority being adults. Right heart catheterization was performed in all. None had an associated congenital or acquired cardiac abnormality.

Sixty-five had defects of the septum secundum, 14 of the septum primum. In the latter individuals there could be palpated, at operation, no septal tissue above the atrio-ventricular valves. In none of these was significant mitral insufficiency found.

Thirteen patients died during surgery or in the immediate postoperative period. Of these, eight had septum primum defects, five septum secundum defects.

At least one preoperative electrocardiogram of each individual was available. In 57 of the survivors, several tracings were secured during the period of hospitalization, postoperatively and at intervals during the succeeding several months. Twenty-one have been followed for at least two years. Postoperative records of nine patients are not at hand.

Thirty-eight were recatheterized following operation, the interval between surgery and the study varying from two weeks to four years, the average being one year. The data in six of these proved that the defect had not been completely obliterated, a fact suspected by the surgeon at the completion of operation.

Eliminating the electrocardiograms of these six, there remained 51 suitable for comparative study. In 32 no shunt was demonstrable postoperatively; in the remaining 19 the surgeon was certain of complete closure of the defect and there existed clinical evidence of this result in that symptoms disappeared, murmurs were no longer present or were markedly altered and other signs were changed for the better.

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**Work done during tenure of Research Fellowship, National Heart Institute.

In the recatheterized patients, attention was given to right ventricular pressure, right ventricular work and to flow index in the light of the electrocardiographic data obtained.

Results

Normal sinus rhythm was present preoperatively in 70 patients, atrial fibrillation in eight and chronic atrial flutter in one. Postoperatively the fibrillation and flutter persisted. In those with normal sinus rhythm who survived, transient atrial arrhythmias were frequently seen in the immediate postoperative period; in all there was reversion to a normal pattern.

In 29 initial tracings the P wave was normal; in the others it was widened, notched or peaked, with a notably tall or biphasic configuration in V_1 or V_2. Postoperatively, abnormalities were more common but there was no significant pattern of change.

The P-R interval was greater than 0.22 second in 15 preoperatively. Three died. Postoperative tracings of two cannot be found. Of the 10 remaining, the interval was reduced in four, increased in one and unchanged in five. In four patients with normal P-R interval preoperatively there was a slight prolongation postoperatively. The defect was proved to be completely closed in each.

Right axis deviation was present in 77 of the original 79. In two who had septum primum defect there was left axis deviation. It must be

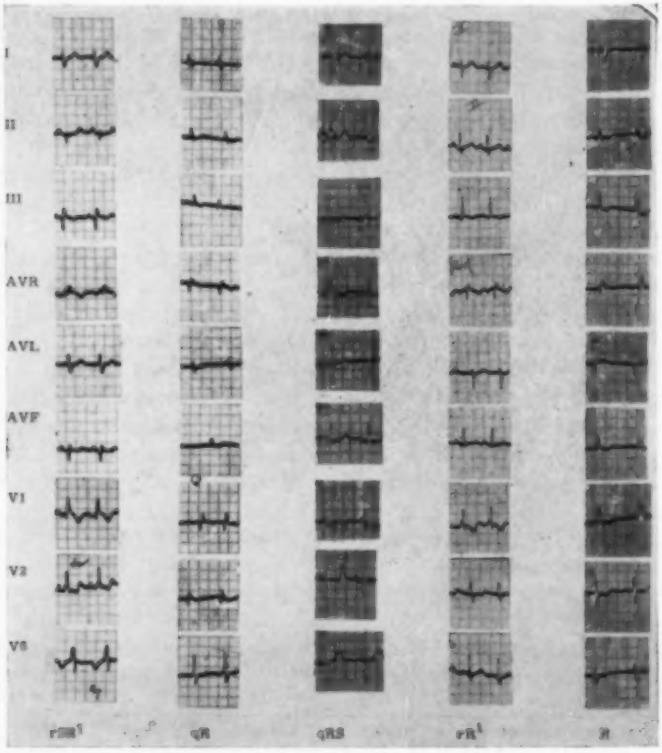

FIGURE 1

stressed that the other 12 with septum primum defect had right axis deviation. Postoperatively, there was a tendency toward a normal electrical axis.

Five basic QRS patterns in V_1 were seen preoperatively: rsR′, qR, rR, R and qRs (Fig. 1). When a qR was present in V_1, an rsR′ was invariably present in V_2. Careful measurement of the QRS duration in V_2 in these cases made it apparent that the initial r in V_1 was isoelectric. The pattern most frequently encountered was rsR′. This was present in 55 patients (75 per cent). In 17 (21 per cent) a qR and in 5 (2.5 per cent) an rR or R were found. An rS in V_1 and V_2 in two patients was considered normal.

The mean duration of QRS in V_1 before surgery was 0.086 ± 0.0016 sec.* (Table 1). The mean amplitude of the R wave was 8.38 ± 0.23 mm.* In 51 individuals in whom it was clinically demonstrated or proved by catheterization that the defect had been completely closed, there was a decrease in QRS duration in 54 per cent (mean 0.079 ± 0.003 sec.*) and in R wave height in 37 per cent (mean 6.52 ± 0.047 mm.*) in tracings secured within a period of two months. During this time an rsR′ pattern persisted in 26 of 38 patients in whom it was present preoperatively. In 6 instances the rsR′ gave way to an RS. Two with rs were unchanged. An rsR′ pattern developed in two who originally had rR. Of the 21 patients

*Standard error of the mean.

TABLE I—COMPARISON OF ELECTROCARDIOGRAPHIC AND HEMODYNAMIC DATA PRE- AND POSTOPERATIVELY

	Preoperative	Postoperative
Right Ventricular Work (Kg/M./Min)		
Mean	0.086	0.079
*SD	±0.014	±0.018
†SE	±0.002	±0.003
Height or R or R¹ (millimeters)		
Mean	8.38	6.52
SD	±2.07	±3.38
SE	±0.23	±0.47
Right Ventricular Pressure (mm. Hg.)		
Mean	46.70	21.54
SD	±2.49	±5.36
SE	±0.29	±0.92
Flow Index (P/S)		
Mean	2.95	Closed
SD	±0.36	
SE	±0.05	
Right Ventricular Work Kg./M./Min.)		
Mean	2.32	0.62
SD	±1.28	±0.42
SE	±0.16	±0.09

*SD — Standard deviation.
†SE — Standard error of the mean.

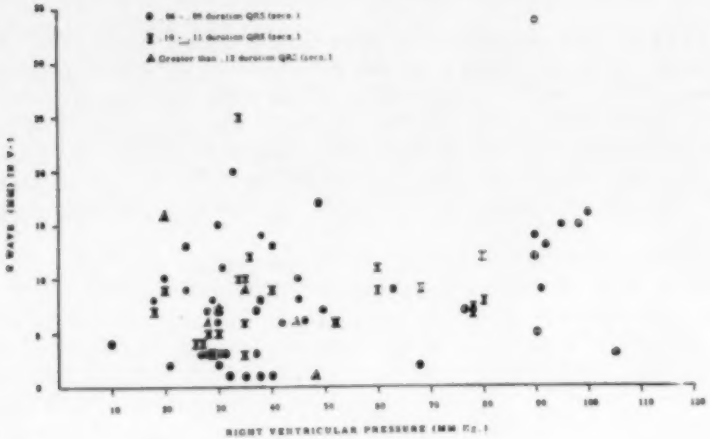

FIG. 2

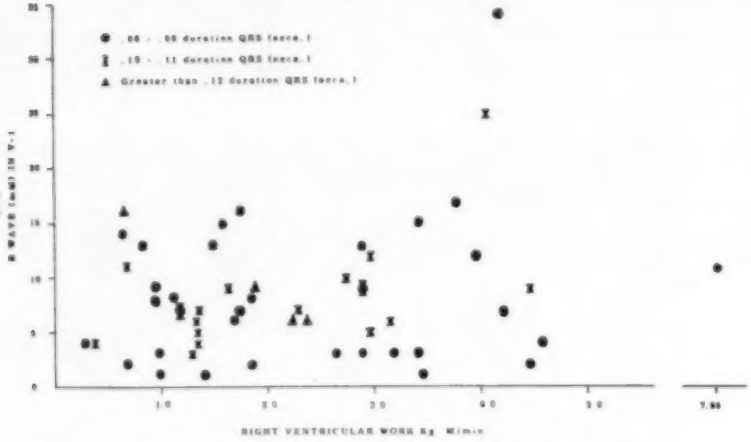

FIG. 3

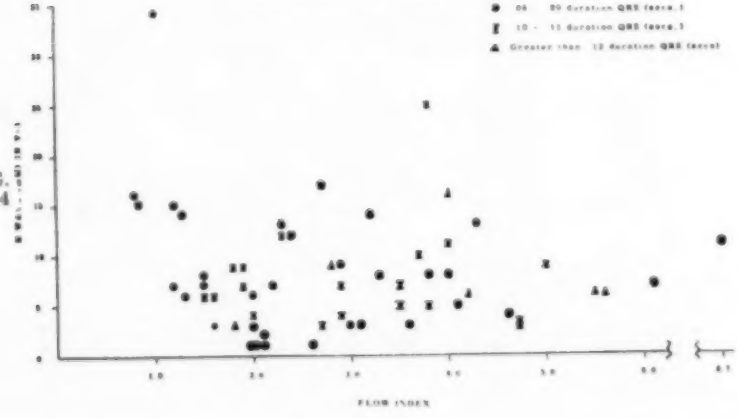

FIG. 4

in whom follow-up observation of at least two years has been possible there were only two in whom there was further decrease in duration of QRS. On the other hand, the height of the R in V_1 continued to decrease in 13.

The common preoperative pattern in V_6 was RS (62 cases, (79 per cent). The S wave was invariably deep and slurred in this group. In eight subjects (10 per cent) rS, and in two (2.5 per cent) R was found. The remaining seven had a qRS, the S wave being deep and slurred in five instances. Postoperatively there was no significant alteration in this lead.

Preoperatively, in the recatheterized group, the mean right ventricular systolic pressure was 42.38 ± 1.27* mm. Hg.; the mean right ventricular work was 2.32 ± 0.16* Kg. M/sec. Following operation the mean pressure fell to 21.5 ± 0.92* mm. Hg. and the right ventricular work to 0.62 ± 0.09* Kg. M/sec. (Table I).

As illustrated in Figures 2 to 4, there was no apparent correlation of QRS configuration or duration or of R wave amplitude in V_1 with right ventricular systolic pressure, right ventricular work or flow index. However, in the five instances in which QRS duration was 0.12 sec. or greater, a large flow index was present.

Comment

The predominant pattern in this group of patients was rsR′, that of delayed conduction in the right ventricle, with or without hypertrophy. For all practical purposes the rR, R and qRs patterns may be considered as rSR′ equivalents although they were not so treated statistically.

Within a few days to a week following closure of the atrial septal defect there was a reduction in the QRS duration and a decrease in the amplitude of the R wave in the right precordial leads (Figs. 5-6). Late, follow-up

*Standard error of the mean.

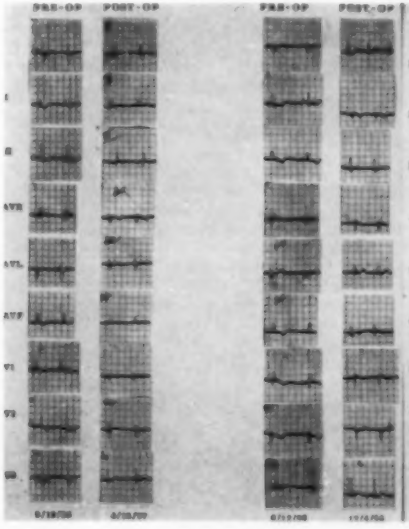

FIGURE 5

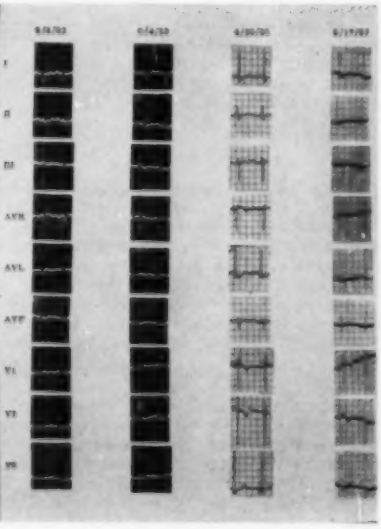

FIGURE 6

electrocardiograms showed some further reduction in R amplitude with little or no further decrease in QRS duration. In spite of obliteration of the shunt and significant reduction in right ventricular pressure and work, in almost all cases QRS in V_1 and V_6 resembled the preoperative configuration.

The rsR′ pattern in atrial septal defect has been ascribed to various causes. If due to hypertrophy of the crista supraventricularis,[2] how explain its appearance in acute right ventricular overload as in pulmonary embolism? Or following pulmonary valvulotomy which has resulted in pulmonary insufficiency?[3] If due, purely, to diastolic overload of the right ventricle,[4] how explain its presence in such lesions as isolated pulmonary stenosis and others[5-7] in which there is a systolic overload? And how relate its persistence in our cases even though there was no longer a diastolic overload?

A factor which is certainly potentially common to all of these conditions is dilatation of the right ventricle. Especially in atrial septal defect of significant size one would expect lengthening of myocardial fibers of the right ventricle to allow it to accept the added volume of the shunt. This serves to increase the length of the fibers of the right bundle and conduction time is therefore prolonged.[8] The immediate decrease in QRS duration following closure of an atrial septal defect suggests that the elasticity component of the stretch has disappeared. The persistence of a degree of widening of the complex may be taken to indicate an irreversible or slowly reversible static stretch. The continuing decrease in R amplitude without further decrease in QRS duration in the late follow-up period probably reflects reversion of hypertrophy of right ventricular fibers.

SUMMARY

The predominant right precordial pattern seen in the electrocardiograms of patients with atrial septal defect is rsR′.

Following closure of the defect there is a decrease in QRS duration and in the amplitude of the R wave. In a two year follow-up in this series there was no progressive diminution in QRS duration although the R wave continued to become smaller.

The data indicate that delay in conduction in the right bundle branch system is due to stretching of the right ventricular muscle fibers and should be considered evidence of dilatation of the chamber.

RESUMEN

El cuadro predominante, precordial derecho que se ve en el electrocardiograma de los enfermos con defecto sepal, es rsR′.

Después del cierre del defecto hay un decrecimiento de la duración de QRS y en la amplitud de la onda R. En seguimiento de esta serie por dos años no hubo disminución progresiva de QRS aunque la onda R continuó haciéndose menor.

Los datos indican que el retardo de la conducción del sistema del haz de la rama derecha se debe a estiramiento de las fibras musculares ventriculares derechas y debe ser considerado como evidencia de dilatación de la cámara.

RESUME

Le tracé précordial droit prédominant dans les électrocardiogrammes des malades atteints d'alteration de la paroi de l'orreillette est rsR′.

Après disparition de l'altération, il y a une diminution de la durée QRS et de l'amplitude de l'onde R. Dans un contrôle de deux ans portant sur cette série, il n'y eut aucune diminution progressive de la durée QRS bien que l'onde R continue à devenir plus petite.

Ces faits indiquent que le temps de transmission dans le système de bloc de branche droit est dû à l'extension des fibres musculaires du ventricule droit et devrait être considéré comme la preuve de la dilatation de la cavité.

ZUSAMMENFASSUNG

Die vorwiegend rechtsseitige praecordiale Form des EKGs, die man bei Patienten mit Vorhof-Septum-Defekten sieht, ist rsR'.

Nach Verschluss des Defektes kommt es zu einer verringerten QRS-Dauer und kleineren Amplitude der R-Zacken. Bei einer zweijährigen Nachbeobachtungszeit dieser Reihe von Kranken zeigte sich keine progressive Verminderung in der QRS-Dauer, obwohl die R-Zacke annaltend kleiner wurde.

Die gewonnenen Werte weisen darauf hin, dass eine Verzögerung in der Leitung des rechten Schenkels des Reizleitungssystems die Folge einer Dehnung des Muskelfasern des rechten Ventrikels ist und als Anhaltspunkt für eine Erweiterung der Kammer angesehen werden muss.

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New Facts Concerning the Circulation in the Lung, Its Control, and Its Interaction with the Systemic Circulation*

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In spite of the massive volume of hemodynamic data which has been collected in humans many basic problems of circulatory physiology, pathology and therapy remain unsolved or controversial. Blood flows and pressures cannot usually be measured, controlled and varied adequately in man; a complete, rational picture of human circulatory physiology is therefore not in existence. Hence the need for fully controlled animal experimentation.

This paper summarizes information which has been accumulated during the past two years, using an experimental preparation which permits fully controlled investigations of the pulmonary and the systemic circulations and of their interactions. It provides for the measurement of pulmonary arterial and venous pressures while the flow of blood through the lung is known and can be regulated (Fig. 1). The lungs of open-chest dogs are perfused in situ from a pump-reservoir circuit after the pulmonary artery is ligated, the ascending aorta clamped, and the systemic circulation of the animal carried on the heart-lung machine. There is no communication between the systemic and the pulmonary circulations, except for the collateral flow in the bronchial vessels. The lungs are innervated and nourished; blood flow through the pulmonary vessels is determined at will by setting the output of a calibrated pump. In addition, the changing blood volumes in the animal and in the pulmonary circuit can be measured by isotope or dye dilution techniques. Collateral blood flow to the lungs is measured by changes of the pulmonary reservoir level and also by isotope dilution. Factors influencing collateral pulmonary flow have already been described in a separate communication.[1]

Pressure-Flow Relationships in the Lungs

Our studies[2] corroborate many previous investigations of pressure-flow relations in the lungs. It is well known by now that progressive increments of pulmonary blood flow do not produce a steadily increasing pulmonary arterial pressure (Fig. 2). As the blood flow through the lungs is gradually increased from zero, there occurs a rather steep rise of the pulmonary artery pressure, but as soon as 25 per cent basal cardiac output is reached the pulmonary artery pressure rises only slightly with further increments of blood flow. This well known relationship has been found to apply in animal and human lungs[3-6] and has been explained by the passive unfolding or dilatation of pulmonary vessels as the flow increases.

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During investigation of pulmonary arterial pressure as a function of blood flow it is essential to control the pulmonary venous pressure. In our experiments the pulmonary venous pressure was kept as constant as possible by draining the flow from the left atrium or from the left ventricle through very wide cannulae (inside diameter ¼″ to ½″); which emptied via a constant outflow resistance into the reservoir (Fig. 3). At high pulmonary flows the pressure in the pulmonary veins increased in spite of the constant outflow resistance; I don't know whether this corresponds with events in the human where changes of the pulmonary venous pressure in exercise are still controversial. (I have found no direct measurements of human left atrial or pulmonary venous pressure during exercise.) Our studies corroborate the well known observation[7, 8] that elevation of the pulmonary venous pressure at constant flow does not cause identical increases of the pulmonary arterial pressure: when the pulmonary venous pressure is increased the blood vessels in the lungs dilate passively and thereby lessen the resistance of the pulmonary circulation. On many occasions we watched for a "protective reflex" in the sense of Dexter et al.[9] (disproportionately greater increase of pulmonary artery pressure after raising the pulmonary venous pressure), but failed to observe it.

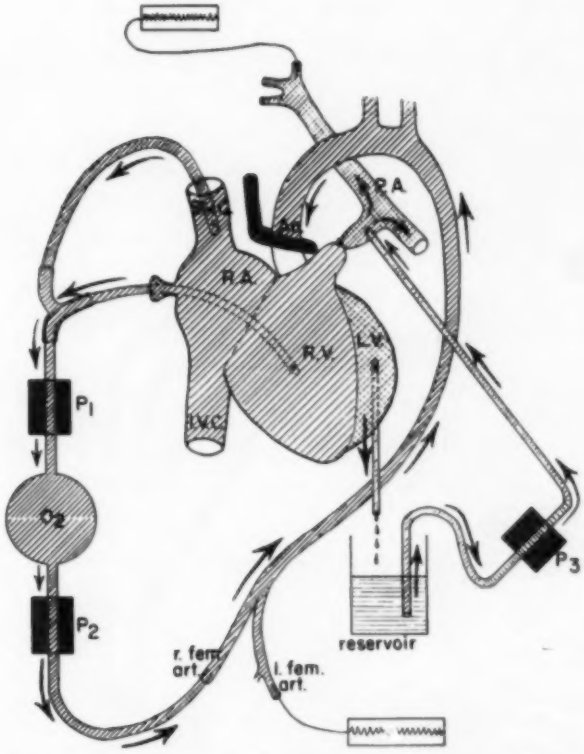

FIGURE 1: Schematic diagram of blood circuits for separate perfusion of pulmonary and systemic circulations, with heart excluded. $P_{1, 2, 3}$—pumps; O_2—oxygenator; PA—pulmonary artery.

We discovered numerous factors which can influence the pressure-flow relationship in the lungs. The temperature of the perfusing blood has an effect on the state of contraction of the pulmonary blood vessels:[10, 11] perfusion of the lungs—but not of the systemic circulation—with cold blood causes large increments of the pulmonary artery pressure (Fig. 4) which are not explained by changes of the blood viscosity. This finding is of possible interest to those who have occasion to use hypothermia; it also warns us to control the blood temperature at all times during our experiments.

The pH of the pulmonary perfusion blood can influence the tonus of the pulmonary vasculature (Fig. 5); the pH of systemic blood is without influence on the pulmonary vessels. Certain drug effects can be observed at one pH but not at another.[18] The effect of breathing 5 per cent or 10 per cent CO_2 is larger than can be explained by changes of blood pH secondary to changes of the alveolar CO_2 tension.[2]

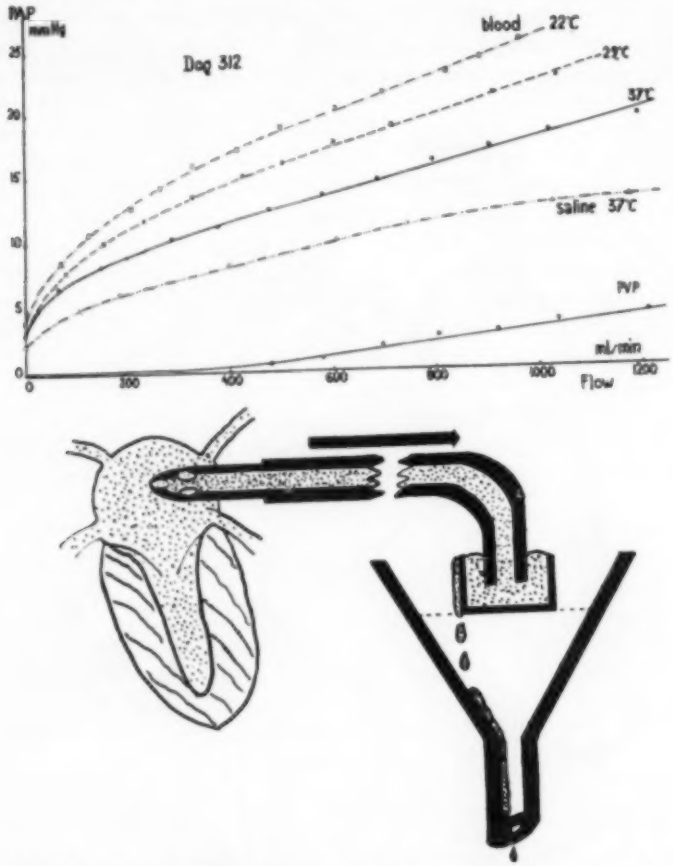

FIGURE 2: Changes of dog's pulmonary artery pressure (PAP) as a function of increasing flow. Effect of temperature on pressure-flow relationship.

FIGURE 3: Arrangement for constant outflow pressure for blood issuing from left atrium or left ventricle.

Our experiments have established the importance of the calcium level of the pulmonary perfusion blood: the pulmonary artery pressure at constant flow is directly related to the level of ionized calcium in the pulmonary, but not the systemic blood.[18]

The airway pressure exerts a pronounced influence on pulmonary artery pressures, but not in the sense which is usually described. When lungs in the open-chest dog are ventilated with changing volumes of air so that the expiratory airway pressure is constant, but the positivity of the insufflation pressure is variable, the inspiratory peaks of the pulmonary artery pressure increase in a direct relation with the inspiration pressure, but the pulmonary artery pressure falls during expiration (even as the "inspiratory" pulmonary artery pressure rises) with progressively increasing airway pressure: the net effect is a mean pulmonary artery pressure which is elevated only slightly or not at all with increasing tracheal pressure (Fig. 6).[2] This finding contrasts with other observations reported in the literature, where the lungs were kept in a state of continued inflation when it was desired to investigate the effect of ventilation on pulmonary vascular resistance.

The effect on pulmonary vascular pressure of pressor amines, of acetyl choline, of histamine, of antihistamine-histamine combinations, of sero-

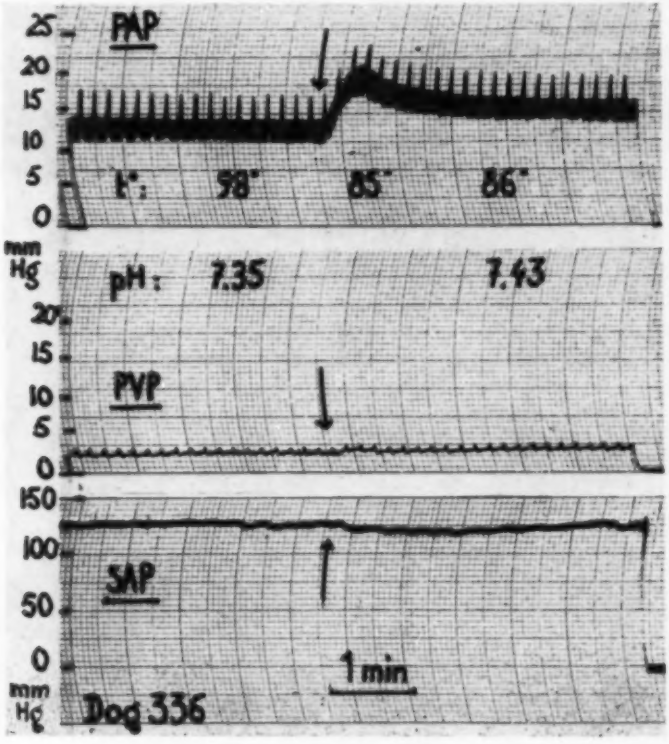

FIGURE 4: Effect of lung perfusion with "cold" blood on pulmonary artery pressure (PAP). PVP—pulmonary venous pressure; SAP—systemic artery pressure.

tonine, of serotonine-antiserotonine combinations has been observed in my laboratory, and reports from other laboratories were confirmed.[19] Hemolysis with saponin or with distilled water did not change pulmonary vasomotor tonus.[18] At normal pH and basal flow only papaverine had a vasodilator effect in our preliminary experiments; vasodilator effects of other drugs, for instance, "B W 4550" could be observed only when the pH of the pulmonary perfusion blood was abnormally low.[18]

The nervous control of the pulmonary vasomotor tonus has long been a matter of argument: some investigators have gone so far as to deny any nervous participation in the maintenance of normal vasomotor tonus in the lungs. If this were so, it would be quite unnecessary to investigate the pulmonary circulation with elaborate and complex preparations such as ours and it would be sufficient for most purposes to perfuse isolated lungs. I have studied the contribution of the central nervous system to pulmonary vascular tonus by observing pulmonary pressures at varying pulmonary flows, first while the heart-lung machine perfused the systemic circulation, and later when the systemic perfusion was arrested. It can be seen (Fig. 7) that with constant pulmonary flow, asphyxia of the systemic circuit (produced by sudden arrest of the heart-lung machine) can cause pronounced changes of the pulmonary vasomotor tonus. These changes must be caused by nervous impulses since systemic blood with its epinephrine and other pressor agents cannot reach the perfused lungs when the peripheral circulation is arrested. The "asphyxia" response of the lung vessels coincides with the generalized asphyxial contraction of the systemic vessels[12] which Starling[13] first observed after sudden arrest of the circulation. The "asphyxia" response must be caused by anoxia of the central nervous system; it is not reproducible when acid is infused into the systemic circulation. As can be seen (Fig. 7), both pulmonary arteries and pulmonary

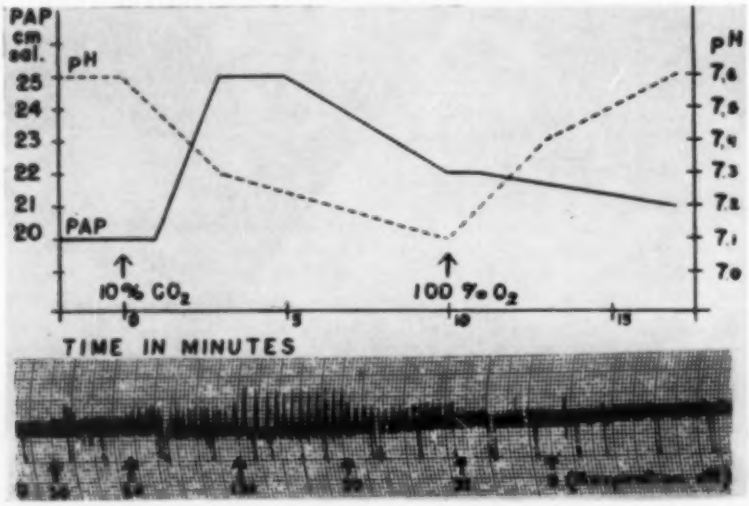

FIGURE 5: Effect of blood pH on pulmonary artery pressure at constant flow.
FIGURE 6: Effect of positive pressure ventilation on pulmonary artery pressure.

veins can contract with asphyxia; this is borne out by the fact that the increment of pulmonary artery pressure with asphyxia and constant flow exceeds the increase of pulmonary venous pressure. The asphyxial contraction of the pulmonary vasculature is always observable but is at times limited to the pulmonary arterioles. The findings presented here suggest that the pulmonary artery pressure at constant pulmonary flow may be related to the oxygen tension in the carotid and other chemoreceptor regions[14] or in the central nervous system. This proposition is now under investigation in my laboratory. If such a correlation of pulmonary arterial pressure and cerebral oxygen tension were found, it could contribute to an explanation of the pulmonary artery pressure changes which are seen in systemic anoxia. Four or five minutes after the arrest of the systemic

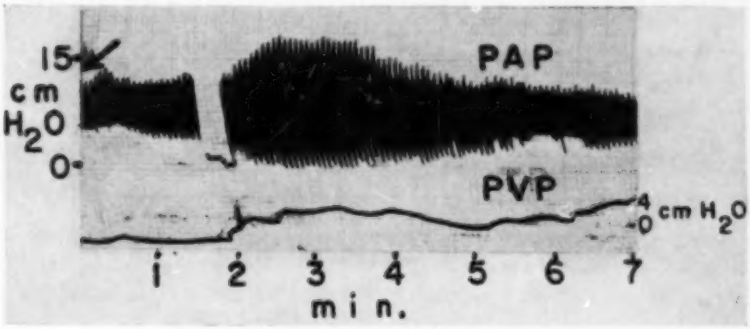

FIGURE 7: Effect of systemic asphyxia on pulmonary artery pressure. Systemic perfusion was arrested at "zero" time while pulmonary perfusion continued unchanged.

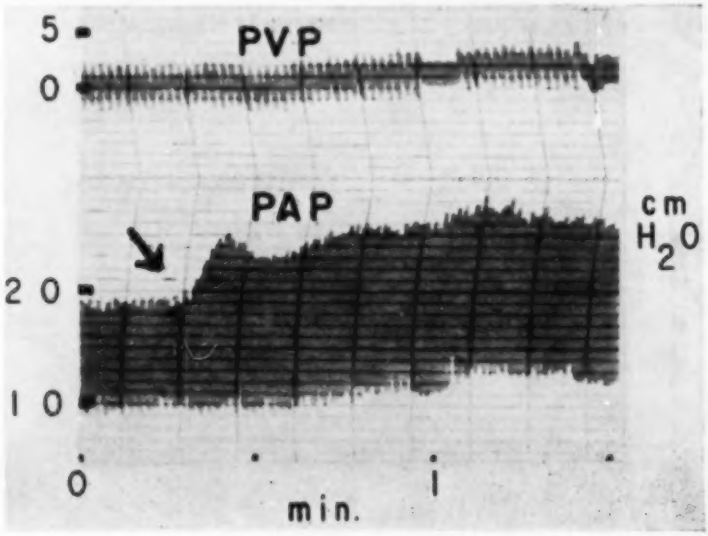

FIGURE 8: Effect of 10 gamma arterenol on pulmonary artery pressure in lung perfused with "cyanided" blood. Drug added at arrow. Pulmonary blood flow constant.

circulation the "asphyxial contraction" of the pulmonary vessels subsides. The pulmonary vascular pressures then either fall to values which are significantly below the control values preceding asphyxia, or they remain elevated. The reason for the totally different behavior of different animals is not yet apparent to us. Pressure-flow curves can now be constructed in lungs which are perfused with oxygenated blood of normal pH and which

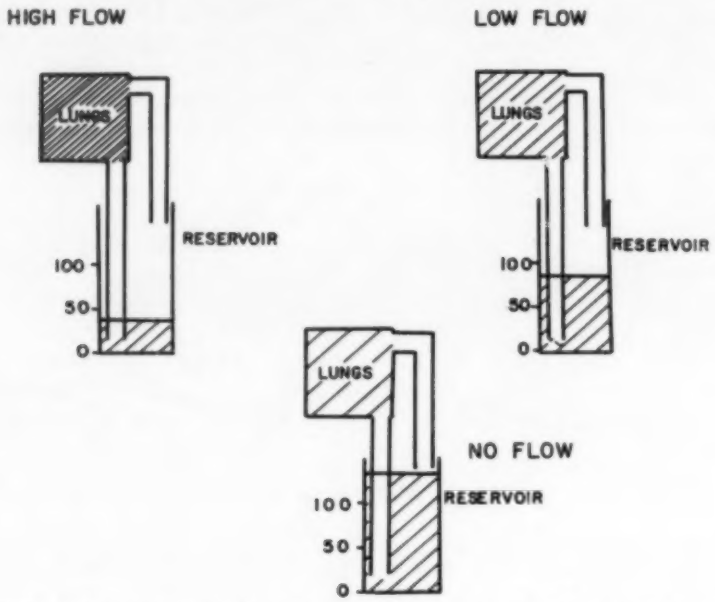

FIGURE 9: Diagram illustrating how total blood volume of pulmonary perfusion circuit is redistributed between lung and reservoir, as a function of flow and other factors.

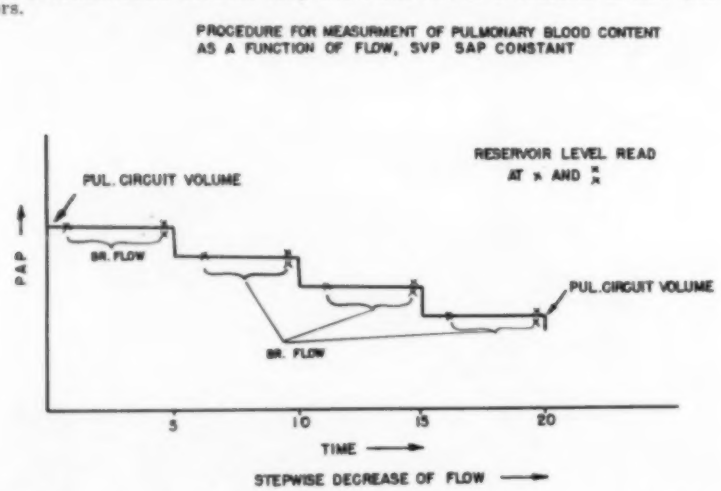

FIGURE 10: Diagram illustrating how pulmonary blood volume can be determined from the rise of the perfusion reservoir level, when bronchial flow to the lung is taken into consideration.

have not been subjected to additional surgical interference or change of spatial relationship but which are now contained in a body without a functioning nervous system. Pressure-flow curves in this "denervated" lung are often strikingly different from the pressure-flow curves previously seen in the same preparation when it was "innervated." However, it is premature to show data because of the variability of the individual preparations.

In our experiments, arrest of the systemic circulation causes the functional absence of the nervous system but it does not asphyxiate the pulmonary vessels, which are still perfused with oxygenated blood. In order to demonstrate the effect of vital processes on vasomotor tonus I injected lethal doses of KCN into the pulmonary circuit. Cyanide causes the immediate arrest of oxidative cell metabolism and therefore should transform the pulmonary vessels into inert tubes. Different individuals of the same species (dog) again show totally differing responses to perfusion of their lungs with cyanided blood: Cyanide causes a marked pulmonary vasodilatation in some, while in others marked pulmonary vasoconstriction occurs. It may be of some interest to know that after cyanide the lung vessels still react to arterenol or serotonin (Fig. 8).

Blood Volume—Flow Relationships in the Lungs

In our preparation there occurs a pronounced change of the blood level in the pulmonary perfusion reservoir whenever the blood flow through the lung is changed. When a correction for collateral flow to the lung is made

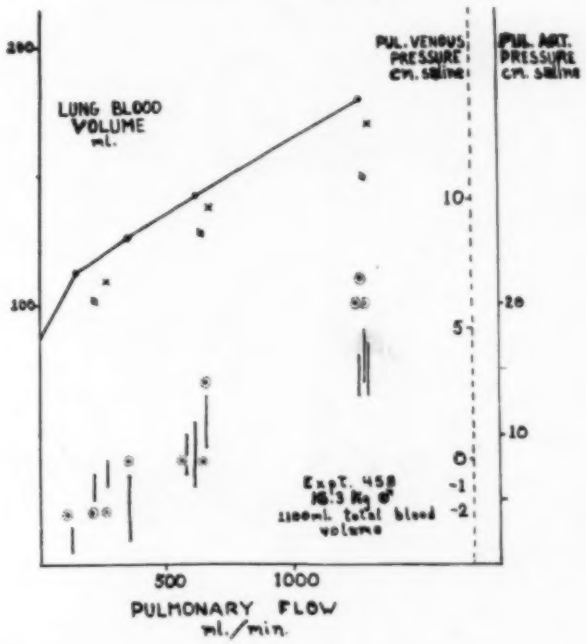

FIGURE 11: Pulmonary blood volume in one dog as related to flow, when the pulmonary venous pressure was permitted to increase with increasing pulmonary perfusion.

(collateral flow is measured for several minutes after a change of pulmonary flow when the systemic arterial and venous pressures are constant), the change in the reservoir level can be used to represent changes of the blood content of the lungs which have occurred as a result of changes of the perfusion rate. This experiment must be performed with control of all pressure variables—systemic and pulmonary arterial and venous pressures, tracheal pressure, blood temperatures and pH, as well as continuous monitoring of the reservoir levels (Figs. 9 and 10) or the reservoir weight.

Preliminary data have shown that the blood content of the non-perfused lung is largely a function of the pressure in the left atrium; with a negative pressure in the left atrium and in the pulmonary veins, such as one might expect with the chest closed, then non-perfused lungs contain as little as 3 per cent of the total blood volume. When the pressure in the left atrium is zero, the blood content of the non-perfused lungs rises to 5—6 per cent of the total blood volume. With increasing perfusion rates but with the pressure in the left atrium held constant or nearly so (manipula-

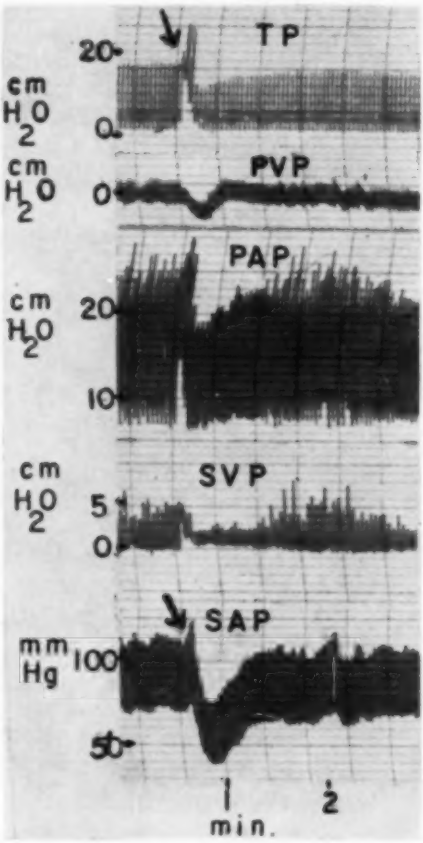

FIGURE 12: Effect of increased airway pressure ("TP") in dog with open chest and intact circulation. Note precipitous fall of systemic artery pressure.

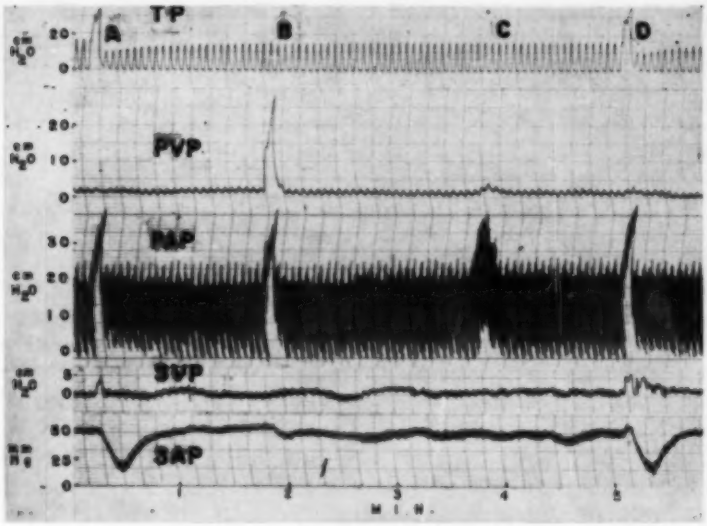

FIGURE 13: Effect of increasing airway pressure ("TP") on systemic and pulmonary pressures at constant flows and double perfusion. Tracheal pressure raised at "A" and "D". Pulmonary artery pressure raised by venous constriction ("B") and by temporary increase of pulmonary arterial flow ("C"), causing relatively small changes of systemic arterial pressure, while increases of airway pressure ("A" and "D") cause marked systemic vasodilatation.

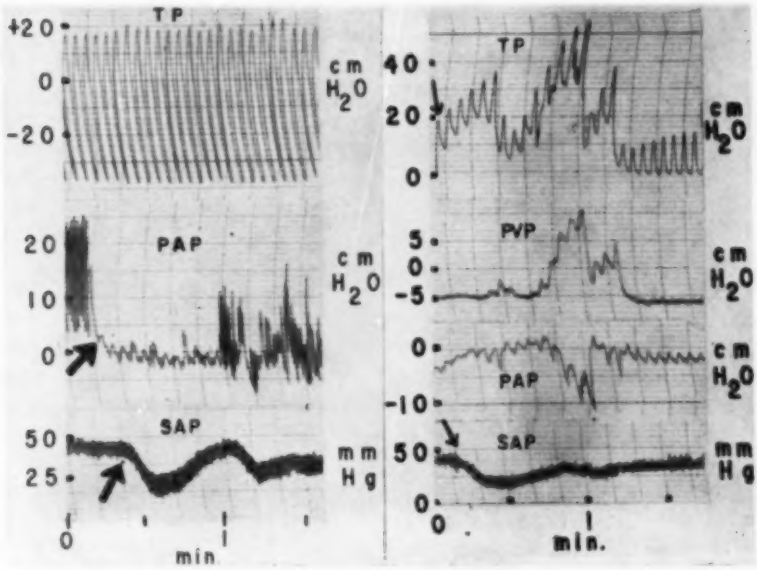

FIGURE 14: Lungs not perfused. Fall of systemic arterial pressure when lung is "pulled" gently (arrow). Systemic flow constant.

FIGURE 15: Lungs not perfused. Fall of systemic arterial pressure without recovery after increased tracheal pressure (arrow). Systemic flow constant.

tion of the constant outflow resistance), the blood content of the lung rises in a curvilinear fashion until it reaches 14 per cent of the total blood volume at a basal flow of 80 ml/Kg/min (Fig. 11). Increasing pulmonary venous pressures can cause massive increases of the pulmonary blood volume. With constant pulmonary flow but rising left atrial (and pulmonary venous) pressure, the blood content of the lung vessels rises steeply. Maximal pulmonary blood volumes were observed with combinations of high flow and high left atrial pressure but such observations were tenuous because pulmonary edema often supervened suddenly when the pulmonary venous pressure was above 25 cm saline. We do not as yet have enough data to describe the pulmonary blood volume at high flows, but in the few cases when high flow was combined with high pulmonary venous pressure (without causing pulmonary edema), it reached up to 35 per cent of the dog's total blood volume.

When pulmonary edema supervened in our experiments the blood volume "trapped" in the lungs could not be recovered. Once pulmonary edema had supervened, continued perfusion even with low flows produced steadily increasing pulmonary artery pressures and eventual blood froth in the trachea—hemorrhagic pulmonary edema.

It should be pointed out that data concerning pulmonary blood volumes in humans are extremely scanty; the increase of the physiological dead space in shock suggests a reduction of the blood content of the human lung which occurs with falling blood flow through the lung.[16] Recent studies of the blood content of the human lung in exercise[15, 16] have suggested a decrease which one would not expect to occur with the increasing blood flow in exercise: we hope to be able to shed light upon this point.

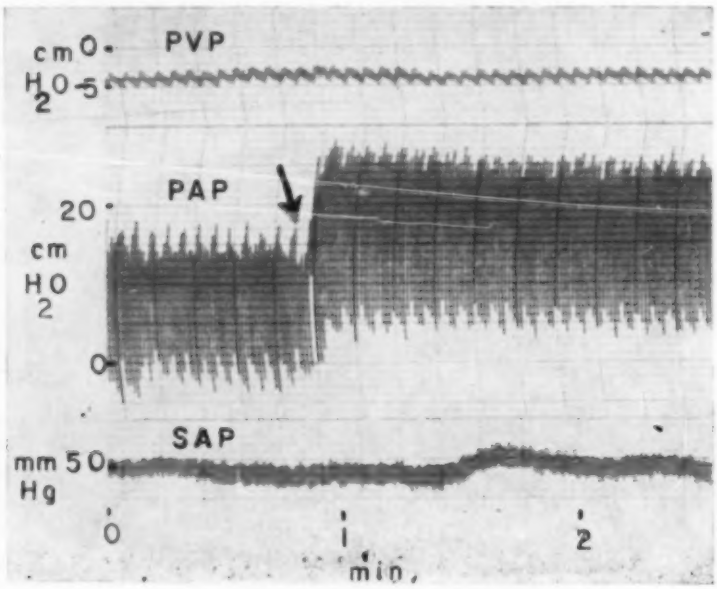

FIGURE 16: Air embolism to perfused lung circuit (arrow) has no significant effect on systemic arterial pressure. Systemic and pulmonary flows constant.

Interactions Between the Systemic and the Pulmonary Circulation

Our preparation lends itself well to the investigation of interactions between the systemic and the pulmonary circulations because we perfuse the two systems with constant, known, predetermined volumes of blood.

It is generally accepted that systemic arterial pressure changes occur after positive pressure respiration because of the changed cardiac output, but we have now shown that increases of airway pressure also have profound effects upon the systemic arterial pressure which are entirely unrelated to the blood flow: when the systemic blood flow is constant, increased airway pressure or gentle mechanical "pulling" of the lung always produces falls of the systemic arterial pressure, regardless of the blood flow through the lung (which may even be absent) and regardless of the positive or negative pressure in the pleural cavities. In some animals this reflex peripheral vasodilatation produced by lung stretch is severe enough to produce a state of shock, and to preclude a return to normal of the systemic arterial pressure even if the perfusion rate is increased (Figs. 12, 13, 14, 15). Blockade or section of the vagi abolishes the reflex peripheral vasodilation which is caused by increased airway pressure or by lung stretch.

It has been shown that increasing systemic venous pressure causes elevated pulmonary artery pressures at constant flow.[2] This effect originates in the right atrium; when a balloon distends it the pressure in pulmonary arteries and veins rises, even as pulmonary flow is constant. I believe that the dilating right atrium "pinches off" the pulmonary veins as they enter the left atrium, in a manner as yet unexplained. This mechanism, if found in man, may explain the occurrence of pulmonary edema in patients with failure of the right ventricle.

At no time did we see simultaneous changes of the pulmonary artery pressure after producing changes of the systemic arterial pressure. We failed to see this relation in well over 150 observations. This is surprising because Daly et al[17] described changes of pulmonary artery pressure ("pulmonary vasomotion"), which occurred after stimulation of the carotid sinus nerves or after elevation of the systemic pressure.

Elevations of the pulmonary arterial or venous pressures often produced slight falls of the systemic arterial pressure (corroborating Daly[20] and Aviado.[21] Air embolism in the perfused pulmonary circuit causes the expected immediate increase of the pulmonary artery pressure but does not usually cause changes in the systemic arterial pressure (Fig. 16). Injection of KCN into the separate pulmonary circulation which the systemic circuits are being perfused causes an immediate fall of the systemic arterial pressure to shock levels, followed by compensatory overshooting of the arterial pressure. This effect occurs without any transfer of cyanide to the systemic circulation and is abolished by vagotomy. It might illustrate the maximum systemic reflex activity which can take place following stimulation of pulmonary receptors.

SUMMARY

An experimental technique developed in my laboratory, permits study of the pulmonary circulation and of pulmonary—systemic interactions, with full control of all variables. Flow-pressure relationships in the pulmonary vascular bed have been

studied. Effects of blood temperature, of blood pH, of inspired CO_2, of positive airway pressure and lung stretch have been found.

Asphyxia of the systemic circulation can cause marked contraction of the pulmonary vessels. "Denervation" of the lungs causes changes in the flow-pressure relationships, indicating a nervous contribution to pulmonary vasomotor tonus.

The blood volume in the non-perfused lung varies between 3 per cent and 5 per cent of the total blood volume, depending on the left atrial pressure. Pulmonary perfusion when the left atrial pressure is near zero can increase the pulmonary blood content up to about 15 per cent of the total blood volume. Simultaneous increases of lung blood flow and of left atrial pressure can cause substantial sequestration of blood in the lungs (up to about 1/3 of the total blood volume).

Increased pressure in the right atrium causes simultaneous pressure changes in pulmonary arteries and veins.

RESUMEN

Se presenta una técnica experimental que permite el estudio de la circulación pulmonar de las mutuas influencias entre las circulaciones general y pulmonar, con un dominio completo de todas las variables.

Se han estudiado las relaciones de la presión del flujo sanguíneo en el lecho vascular pulmonar. Se encontraron los diversos efectos de la temperatura de la sangre, del pH sanguíneo, de la posición positiva en el aire broncopulmonar, y de la expasnsión pulmonar.

La asfixia de la circulacióng eneral puede producir una contracción marchada de los vasos pulmonares. La "denervación" de los pulmones causa cambios en las relaciones del flujo sanguíneo presión indicando que existe una contribución nerviosa en el tono vasomotor pulmonar.

El volumend e la sangre en el pulmón no perfundido, varía entre 3 por ciento y 5 por cieto del total del volumen de la sangre dependiendo de la presión atrial izquierda.

La perfusión pulmonar cuando la presión atrial izquierda está cerca de cero, puede aumentar el contenido sanguíneo pulmonar hasta alrededor de 15 por ciento del total del volumen sanguíneo.

El aumento simultáneo del flujo sanguí pulmonar y de la presión atrial izquierda, puede causar el secuestro de la sangre en los pulmones (hasta alrededor de 1/3 del total de volumen sanguíneo).

El aumento de la presión atrial derecha produce cambios simultáneosde la presión en las arterias y en las venas pulmonares.

RESUME

L'auteur présente une technique expérimentale qui permet l'étude de la circulation pulmonaire et les interactions pulmonaires organiques, avec plein contrôle de toutes les variantes. Les relations débit-pression dans le lit vasculaire pulmonaire ont été étudiées. L'auteur a établi les effets de la température sanguine, du pH sanguin, du gaz carbonique inspiré, de la pression positive de l'air et de l'élasticité pulmonaire.

L'anoxie de la circulation générale peut causer une contraction importante des vaisseaux pulmonaires. La "dénervation" des poumons provoque des altérations dans les relations débit-pression, indiquant une contribution nerveuse au tonus pulmonaire vasomoteur.

Le volume sanguin dans le poumon non irrigué varie entre 3 et 5% du volume sanguin total, dépendant de la pression de l'oreillette gauche. La perfusion pulmonaire, quand la pression de l'oreillette gauche est voisine de zéro, peut augmenter le contenu sanguin pulmonaire jusqu'à environ 15% du volume sanguin total. Les augmentations simultanées du débit sanguin pulmonaire et del a pression de l'oreillette gauche peuvent provoquer une stagnation importante de sang dans les poumons, jusqu'à environ 1/3 du volume sanguin total).

L'augmentation de la pression dans l'oreillette droite provoque des modifications simultanées de pression dans les artères pulmonaires et les veines.

ZUSAMMENFASSUNG

Eine experimentelle Technik in der dargestellten Art ermöglicht die Untersuchung des Kleinen Kreislaufs und der Wechselwirkungen zwischen Lunge und Körper mit voller Kontrolle aller veränderlichen Strömungen und Drucke in der pulmonalen Gefässbahn. Es fanden sich Auswirkungen der Temperatur des Blutes, seines pH-Wertes der eingeatmeten CO_2, und eines positiven Druckes in den Luftwegen.

Sauerstoffmangel im Körperkreislauf kann die Ursache för eine beträchtliche Kontraktion der Lungengefässe sein. "Denervation" der Lungen führt zu Veränderungen in den Beziehungen zwischen Durchströmung und Druck und zeigt so eine nervale Komponente beim pulmonalen Vasomotorentonus an.

Das Blutvolumen in der nicht durchströmten Lunge schwankt zwischen 3% und 5% der gesamten Blutmenge in Abhängigkeit vom Druck im linken Vorhof. Bei gleichbleibendem Blutstrom im Kleinen Kreislauf kann ansteigender Druck im linken Vorhof die pulmonale Blutmenge steigern bis auf ungefähr 15% der gesamten Blutmenge. Eine gleichzeitige Zunahme der Durchströmung der Lunge mit Blut sowie des Druckes

im linken Vorhof Kann eine beträchtliche Blut stauung in der Lunge zur Folge haben. (bis zu ungehähr 1/3 des totalen Blutvolumens).

Eine Zunahme des Druckes im rechten Vorhof führt zu gleichzeitigen Druckänderungen in den Lungenarterien und Lungenvenen.

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Chronic Occlusion of Aortic Arch Branches*

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Partial or complete occlusion of aortic arch branches has commonly been considered a single entity,[9] though it is readily subdivided into a number of distinct types. The classical variety, an idiopathic arteritis (Takayasu's disease or "pulseless disease") which occurs in young women is quite rare.[1, 8] Occlusions resulting from arteriosclerosis obliterans,[2] thoracic outlet syndrome,[14] embolus, aneurysm, dissecting aneurysm, syphilis, Buerger's disease, neoplasm, and thrombocytosis[13] have all been recognized clinically and several are more important than the "pulseless disease" of young women. Incomplete examples of the syndrome are more common than complete ones and this probably explains to a considerable extent the lack of attention that has been given to this group of conditions. Since they are potentially disabling and may lead to death, they deserve careful scrutiny. In addition, it is now possible in most instances to make a proper etiological and anatomic diagnosis and in some cases to perform corrective surgery. In other cases medical treatment appears to be of benefit.

The case studies to be presented are in no way typical but rather exemplify the wide variety of clinical manifestations that may be encountered.

Case Reports

Case 1: E. F., a white woman aged 25, was first seen in 1949 with complaints of dizzy spells and fainting of eight months duration following pregnancy. She stated that pulse and blood pressure readings had always been difficult to obtain in her upper extremities. Three years before, following a pregnancy which terminated spontaneously at full term, she had severe but transitory pain in the left side of her neck posteriorly radiating to her head. A second pregnancy terminated normally seven months before. During labor she noted pain identical to that of the previous pregnancy. Following delivery she "went into shock" and a laparotomy was performed because rupture of the uterus was suspected, but no abnormality was found. She remained in a shock-like state for five or six days then regained consciousness. Three weeks after delivery she began to have episodes of pain in the right posterior neck radiating to the occiput, occurring every two or three days and lasting a few minutes to an hour. About four weeks after delivery she began to feel weak and dizzy on arising in the morning or when standing up quickly and on several occasions experienced brief periods of unconsciousness. She also had frequent episodes of dyspnea and infrequent occurrences of nocturnal dyspnea.

The general physical examination was within normal limits. Heart sounds were clear and the rate and rhythm were normal. A loud, rough, blowing systolic murmur with a gentle diastolic component was heard well in the pulmonary area but even more prominently above the left clavicle. It was transmitted up the left side of the neck and was accompanied by a systolic thrill. Changing from the recumbent to the sitting position produced a pulse rise from 80 to 130. Carotid pulsations could not be felt. The left radial pulse was weak and inconstant. The right was not palpable. No blood pressure could be obtained in the right arm, but it was 120 mm. of mercury systolic and 90 mm. diastolic in the left arm. Femoral, dorsalis pedis, and posterior tibial pulses were normal bilaterally and the blood pressure in each leg was 150 mm. systolic by palpation.

Extensive laboratory and x-ray examinations were within normal limits except for an angiocardiogram which showed a dilated pulmonary artery and a distinctly abnormal aorta. There was the suggestion of a single branch arising from the proximal end of the transverse arch and it was thought that the infundibulum of a patent ductus arteriosus could be seen.

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It was decided that cardiac catheterization and retrograde aortography should be performed, but the catheterization was chosen first. Shortly after the cardiac catheter had been introduced into the right ventricle, ventricular fibrillation occurred. After 45 minutes of manual cardiac compression and artificial respiration a normal rhythm was restored with electric shock. Recovery was complete and uneventful but she declined further diagnostic procedures. A communication to McKusick nearly three years later advised that she was well and without symptoms.[2]

At the time this patient was seen (November, 1949) the diagnosis was thought to be patent ductus arteriosus and a congenital anomaly of the vessels arising from the aortic arch. Subsequent reconsideration by Ross and McKusick[13] and by ourselves has suggested instead that this is a case of classical "pulseless disease" showing a rather slow progression. There is no known congenital anomaly which will result in the loss of both subclavian and carotid pulses, and pure cases of Takayasu's disease may have murmurs indistinguishable from those of patent ductus arteriosus except that the transmission is unusually high. Such murmurs are probably due to collateral circulation. The degree of collateral circulation to the brain, in fact, is attested to by the fact that this patient survived, without apparent brain damage, cardiac massage of 45 minutes which indicates that there was sufficient blood flow even under these trying circumstances. This case has been reported more fully elsewhere.[10]

Case 2: P. L., a 45 year old man, was seen in September, 1956 with a complaint of sudden onset of aching pain in the left shoulder while shelling butter beans. This lasted several hours and recurred the following day when it was accompanied by some pain and numbness in the arm. He was seen at that time and noted to have a weak to absent left radial pulse with a blood pressure on the right of 170/70 and on the left of 120/90. X-ray films and electrocardiogram were within normal limits. For a time there were intermittent episodes of pain occurring mainly at rest and after three weeks this pain disappeared, but on exertion, especially on walking up steps, an aching discomfort was noted in the left side of the neck and along the clavicle.

Physical examination revealed no palpable pulses in the left upper extremity. No bruits, thrills or murmurs were noted. Examination of the heart and lungs was within normal limits, as was the remainder of the examination. There was no neurologic change in the left upper extremity.

Laboratory examinations, including a Master's test, were within normal limits except for a cholesterol of 314 mg. per cent and moderate osteoarthritis of the cervical spine. Oscillometric examination of the upper extremities showed a maximum deflection on the left of one division at 80 mm. of mercury compared to 3.5 divisions at 100 mm. on the right.

It was thought that he had a partial or complete occlusion of the proximal portion of the subclavian artery. The diagnosis of scalenus anticus syndrome was seriously entertained, although no cervical rib was present. It was felt unlikely that he had had an embolus secondary to a myocardial infarction or that the pulse deficit was the result of a dissecting aneurysm or tumor. A catheter arteriogram was performed by inserting a polyethylene catheter percutaneously into the right femoral artery. Films clearly revealed a complete block of the first portion of the subclavian artery about 5 mm. in length with narrowing and irregularity both proximal and distal to the block (Fig. 1). The innominate artery showed no narrowing nor did its branches including the vertebral, right subclavian, and right carotid appear abnormal. The left carotid artery, however, showed slight narrowing of its mouth on the left side. Films of the descending aorta showed no displacement or thickening of the wall, effectively ruling out a dissection (Fig. 2). Laminagrams through the area of occlusion indicated the presence of some calcification. Because the mouths of two vessels were involved, it was felt that this could not represent a thoracic outlet problem.

It was thought at the time that endarterectomy or grafting should be reserved for any sign of progression but additional experience has been gained since this patient was seen. It is our opinion that he has arteriosclerosis obliterans with complete occlusion of the left subclavian artery and early partial occlusion of the left common carotid artery. Endarterectomy is probably the procedure of choice and is almost certainly indicated in this case, even though there has been no progression of symptoms in approximately a year. Reconstitution of the arterial lumen would provide a safety factor by preventing propagation of the thrombus and by providing additional collaterals should occlusion occur elsewhere.

Case 3: V. S., a 36 year old white woman with diabetes mellitus was found in the course of a routine examination to have no pulses in the lower extremities. There had been moderate frontal headaches and nervousness but no other symptoms. The diabetes had been well controlled.

Examination revealed that the blood pressure in the right arm was 190/110. No blood pressure could be obtained in either the left arm or the right leg. The left radial pulse and the lower extremity pulses could not be felt. A loud rough systolic murmur could be heard at the base of the right neck and more faintly over the back but there was no precordial murmur. A pulsation could be felt in the abdominal aorta.

Laboratory findings included a positive Kline and several slightly elevated fasting blood sugars. X-ray films of the chest showed the heart within normal limits of size.

There was a faint suggestion of rib notching and it was thought that a poststenotic dilatation of the descending aorta was present on oblique chest films with barium swallow. The maximum oscillation in the right arm was 2.5 divisions at 140 mm. of mercury, 0.8 divisions in the left arm at 100 mm., and 0.5 divisions at 80 mm. in the right thigh.

It was felt that her condition represented a variant of coarctation of the aorta with narrowing of the left subclavian artery or a coarctation proximal to this vessel. No preoperative contrast studies were carried out. She was explored in February 1957 and found to have a complete occlusion of the left subclavian artery by an arteriosclerotic process. There was some narrowing of the left carotid as a result of a similar process. An arteriosclerotic plaque was also present in the mouth of the innominate artery and in the distal aortic arch. The abdomen was examined through a transdiaphragmatic incision and the abdominal aorta was found to be more or less completely occluded from a point just distal to the renal arteries. An arteriogram performed on the table showed patency of the distal iliac vessels and confirmed the abdominal occlusion. An uneventful left subclavian endarterectomy was performed with reappearance of the left radial pulse (Fig. 3). Eight days later the abdomen was explored and after freeing the distal aorta it was discovered that the patency in the distal iliac vessels was entirely segmental. Distally there was complete occlusion of the external iliac, hypogastric, common femoral, deep femoral, and superficial femoral bilaterally. Extensive endarterectomies were performed on all of these vessels with good back flow except from the superficial femoral artery. It was felt that the block in this extended considerably further than the endarterectomy. After excision of the aorta it was discovered that there was a large partially occluding plaque in the orifice of the left renal artery and in attempting to remove this, the artery was torn. Consequently, a cuff of lyophilized graft previously excised bearing a renal branch was resutured to the main graft. The stump of the left renal artery was anastomosed to the graft branch without difficulty. Distally the anastomoses were made in the common iliac.

Postoperatively, because of the extensive endarterectomies, she was placed on heparin. She developed a large retroperitoneal hematoma which eventually led to obstruction of the ureters by pressure and necessitated re-exploration and evacuation four days later. Her course has been uneventful since that time. Urine output from the

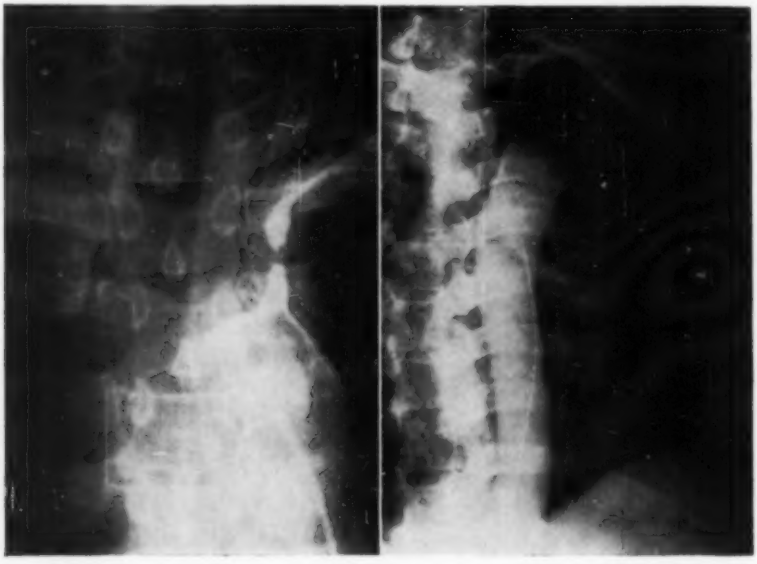

FIGURE 1 FIGURE 2

Figure 1 (Case 2): Transfemoral catheter arteriogram with the catheter at the mouth of the left subclavian artery. Contrast material—70% Urokon, 10 cc. There is a complete block of the first portion of the artery extending for 5 mm. Adjacent to the block there is irregularity of the arterial wall. The other aortic arch branches showed slight narrowing also.—*Figure 2 (Case 2):* A film of the descending aorta made by withdrawing the catheter slightly showed no displacement or thickening of the aortic wall, thus ruling out the possibility of dissecting aneurysm.

left kidney was found to be excellent as early as five days postoperatively despite a renal ischemia of more than 30 minutes. She was able to return to work within a month and has subsequently remained in good health. There has been slight improvement in the oscillometric readings in the lower extremities with a maximum deflection of 1.4 units at 100 mm. of mercury in the right thigh and 0.6 units at 120 mm. in the right calf. An excellent pulse has persisted in the left arm.

Special studies to determine any possible atherogenic predisposition have been unrevealing. Serum cholesterol, 17-ketosteroids, 17 hydroxycorticoids, and fractional proteins have been within normal limits. All of the excised arterial tissue showed severe arteriosclerosis obliterans. There has been no suggestion of syphilitic arteritis. It is planned to carry out further surgery on the superficial femoral arteries if studies show the blocks to be segmental.

This patient undoubtedly suffers from premature atherosclerosis and is reminiscent of a case explored by Blalock and reported by Ross and McKusick.* The cases paraded as slightly atypical coarctations of the aorta and illustrate again that atypical findings are an indication for preoperative aortography. The ease with which endarterectomy may be performed in the subclavian artery was demonstrated in our patient. Similar ease should be experienced in performing endarterectomy for complete occlusions of any of the aortic arch branches. Some caution, however, should be exercised in performing endarterectomies in incompletely blocked vessels, as cerebral damage may result.

Case 4: E. D., a 62 year old railway conductor, was seen after herniorrhaphy was performed elsewhere for a routine physical examination to see if he should be returned to duty. He had no symptoms referable to his upper or lower extremities or any symptoms suggestive of chronic carotid occlusion.

Physical examination revealed absent radial pulse in the right arm, a faint thrill over the base of the right neck, and a blood pressure of 92/80 in the right arm compared to 130/90 in the left arm. A definite bruit was heard at the base of the neck. No subclavian or axillary pulsation could be made out. The right common carotid pulsation was much weaker than the left. There were no positional findings suggestive of a thoracic outlet problem. Oscillometric examination of the upper extremities revealed a maximum excursion of 1.5 at 80 mm. of mercury in the right arm compared to a maximum of 4.5 at 100 mm. on the left side. Pulses, blood pressures and oscillometric readings were within normal limits in the lower extremities. No abnormality of the heart or lungs was noted.

Roentgen examination of the chest showed some tortuosity of the aorta consistent with his age. The heart was unenlarged. There was no cervical rib.

*Case E. L. p. 707.[13]

FIGURE 3 *(Case 3):* Photomicrograph of endarterectomy specimen showing its clearly arteriosclerotic character. Compare to Figure 4 (x 10). Courtesy Armed Forces Institute of Pathology.

A diagnosis of arteriosclerosis obliterans involving the innominate artery or more probably the right subclavian and right common carotid arteries separately was made. Since there were no symptoms and the carotid itself was definitely patent, surgical intervention was considered inadvisable. It is our opinion that endarterectomies in arteries incompletely blocked such as the common carotid will be much more dangerous than similar procedures on arteries already completely occluded. Although this may eventually turn out to be improper reasoning, there is at present no precedent on which to base other conclusions. He will be followed at intervals and surgery will be recommended if any symptom of carotid occlusion develops.

DISCUSSION

Etiology

Congenital anomalies rarely result in complete occlusion of aortic arch branches.[16] Aortic arch anomalies including double arches do not cause absence of pulses. Patent ductus arteriosus may lead to a slight diminution, but not to an obliteration of the pulse. Several well authenticated cases of classical "pulseless disease" have had murmurs in the high anterior chest thought to be due to patent ductus arteriosus. These murmurs may be due to collateral circulation.[12] It is, therefore, possible that cases considered to be patent ductus that have an absent radial pulse may be pure idiopathic arteritis with occlusion. Coarctation of the aorta may be accompanied by differences in pulse or blood pressure in the two arms, but an absent pulse in the left arm is probably found in less than 5 per cent. This may be caused either by a coarctation situated proximal to the left subclavian or by concomitant narrowing of the left subclavian artery.[13] Origin of both subclavian arteries distal to a coarctation with absent pulse in all four extremities has been reported.[15] An absent carotid pulse is probably a very rare finding in congenital malformations and the absence of carotid and subclavian pulses on the basis of congenital malformation probably does not occur.

The most important and best known variety of arteritis which may lead to aortic arch branch occlusion was described by Takayasu in 1908.[17] Although about 100 cases have been recognized, only a few have been from the United States.[1, 8, 18] A disease

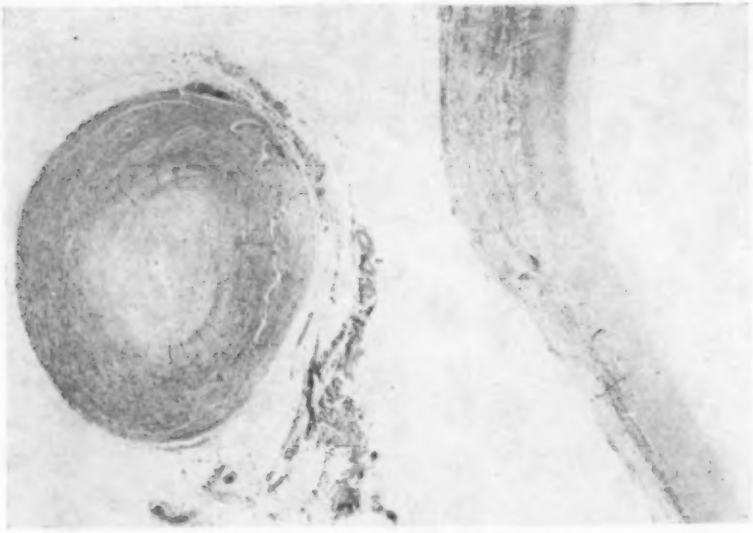

FIGURE 4A FIGURE 4B

Figure 4: Photomicrographs from a case of classical "pulseless disease." Courtesy Armed Forces Institute of Pathology.—*Figure 4A:* Transverse section left common carotid artery. Note the massive intimal and adventitial thickening. The lumen is slit like. A severe arteritis and periarteritis were present. The findings are quite distinct from those of arteriosclerosis (atherosclerosis) (x 6½).—*Figure 4B:* Longitudinal about 4 cm. above the aortic valve. The gradual transition from a relatively normal aortic wall to one showing intimal and massive adventitial thickening is clearly shown. The basic pathology is similar to that seen in the left common carotid artery. Compare to Figure 3 (x 6½).

of young women, it is insidious in onset and results primarily in aortic arch branch occlusions, but may be more widespread. Ocular and cerebral symptoms predominate. The course may be short or long with death the usual outcome. The distinctive pathology is shown in tissue from a 16 year old female with sudden onset of symptoms six months prior to death (Fig. 4).* This patient initially showed a marked change in the pulse pressure of the left arm and clinically was thought to have a coarctation of the aorta. At autopsy the subclavian arteries were occluded and the thickness of the aortic and carotid wall was in places increased to as much as 8 mm. Changes in the aorta extended from 4 cm. above the aortic valve to just beyond the ostium of the left subclavian artery. These changes are grossly and microscopically distinct from those of atherosclerosis.

Syphilitic arteritis may result in narrowing[12] (Fig. 5) or occlusion of aortic arch branches as well as coronary ostia and this may occur in the absence of aneurysm.[13] Other types of arteritis which are rare causes of occlusion of aortic arch branches include "giant cell" arteritis and Buerger's disease.[13]

Arteriosclerosis obliterans (atherosclerosis) is a not uncommon cause of occlusion of one or more aortic arch branches. Undoubted examples involving the common carotid artery are not infrequent in the neurologic literature.[2] Kinney reported a case as an arteritis which on autopsy proved to be arteriosclerotic.[9] It would be our expectation that this group will eventually be the most important one with many presently unrecognized cases.

Repeated trauma or trauma superimposed on a previously diseased artery may result in thrombosis. In the thoracic outlet syndrome there may be chronic trauma to the subclavian artery. Schein, Haimovici, and Young collected 30 cases of arterial thrombosis associated with cervical rib.[14] Eleven of these developed minor gangrene, two required major amputation, and three developed hemiplegia from extension of the occlusion into the carotid artery. On rare occasions thrombosis may result from trauma of effort. Direct trauma to any large vessel may result in thrombosis but this occurs infrequently.

Pressure from an arterial aneurysm may cause narrowing of an artery but without

*Courtesy Dr. Pelayo Correa, University of California and Dr. William C. Manion, Armed Forces Institute of Pathology, Washington, D. C.

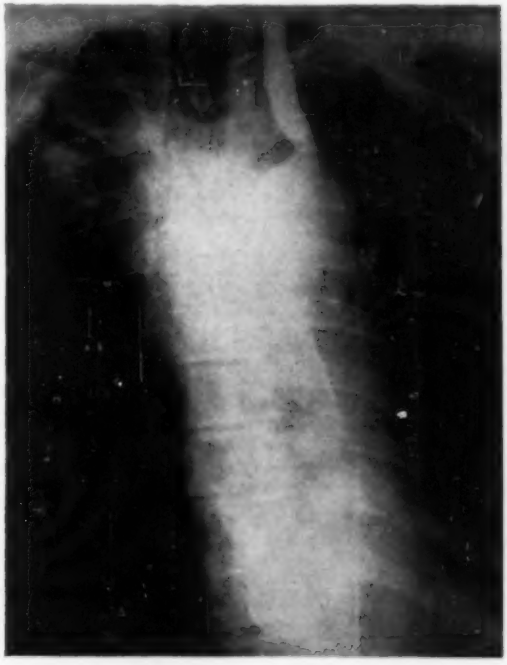

FIGURE 5: Transfemoral catheter arteriogram in a 64 year old Negro male with an aneurysm of the arch of the aorta. There is constriction of the base of the left common carotid artery probably due to syphilitic arteritis.

superimposed thrombosis, propagation of laminated clot, or severe syphilitic arteritis, occlusion is rare.

In occlusion due to arterial embolus, the block will generally be somewhat more distal than the ostia of the aortic arch branches but even multiple proximal occlusions may occur.[10]

Neoplasms may cause arterial occlusion by pressure or by invasion, but such occlusions are quite rare.

Conditions with hypercoagulability of the blood can cause occlusions of aortic arch branches, but, generally, these are in smaller vessels.[10]

We have seen benign thrombosis after the use of the subclavian artery for catheter arteriography.[11]

Unequal pulses are a not uncommon result of dissecting aneurysm but complete loss of pulsation of an aortic arch branch is apparently infrequent. Reports can be found in the literature, however, of occlusion of any or all of these vessels by a chronic dissection.[10]

Symptoms and Course

The exact symptoms depend on the underlying anatomical nature of the occlusion, the etiological cause, the presence or absence of additional small vessel occlusions, age, sex, and the status of the collateral circulation. It is not surprising that both symptoms and course are extremely variable.

Unilateral chronic common carotid artery occlusion commonly results in syncopal attacks, seizures, mental deterioration, and a variety of visual defects. Persistent or episodic hemiplegia, facial atrophy, gangrene, hearing loss, claudication of the muscles of mastication, etc., may also occur. Bilateral common carotid occlusions are similar but symptoms are usually more severe and more frequent, and the disease is more likely to progress to death. The syndrome of internal carotid occlusion is essentially indistinguishable.[5]

Although occasionally asymptomatic, chronic subclavian occlusions generally result in decreased work tolerance, shoulder or arm pain precipitated by exercise, and in severe cases, atrophy or gangrene. There is also danger of extension of the disease to the common carotid artery. Obstruction caused by chronic trauma to the subclavian artery is likely to produce more severe symptoms because of concomitant spasm.[14]

Diagnosis

Chronic occlusion of the aortic arch branches must be kept in mind in the differential diagnosis of a very large group of conditions including angina pectoris, chronic dissecting aneurysm, neoplasm of the chest, cervical disc, musculoskeletal disorders of the shoulder girdle, temporomandibular joint syndrome, and numerous conditions involving the eyes or brain. Once suspected, it will usually not be difficult by careful physical examination to rule it in or out.

Blood pressure and pulse changes are of prime importance. Bruits in the axilla and at the base of the neck will often aid in localization of partial occlusions. Careful neurologic examination and especially competent examination of the eyes is of extreme importance.[5, 10]

Where there is a possibility of direct surgical treatment, contrast visualization is recommended. This can be done by angiocardiography or more precisely by direct aortography. Transfemoral catheter aortography is probably the most valuable single method (Figs. 1 and 2).[11]

Treatment

Methods of treatment and their indications are slowly evolving. There is a great deal of misconception. The usual teaching, for instance, in regard to emboli causing occlusion in the upper extremities is that such emboli are not dangerous and need not be removed. Recent studies indicate that there is a very considerable incidence of gangrene and subsequent disability and that removal of the emboli should generally be undertaken.[15] Partial asymptomatic occlusions probably do not justify either prolonged medical or surgical therapy at this time, though further knowledge may bring a more vigorous approach. In complete occlusion, even where asymptomatic, the danger of progression is such that treatment should probably always be given serious consideration. Where symptoms are prominent, of course, treatment should be carried out whenever possible.

The most useful and increasingly used medical treatment is long term anticoagulant administration.[10] Where surgery is unduly difficult or contraindicated this method is worthy of trial.

Sympathectomy and simple excision of the occlusion have been carried out a number of times without apparent benefit.[16] An exception is subclavian excision for occlusion secondary to the trauma of a cervical rib where improvement had been reported presumably on the basis of decreased arterial spasm.[14]

The more promising methods of treatment are concerned with restitution of arterial blood flow and increasingly frequent reports are beginning to appear in the literature.[5, 6-7] The two main methods available are endarterectomy and the use of an arterial graft. The method should be chosen with regard for the particular anatomical

problem and for the experience of the surgeon. Endarterectomy is probably best suited to short occlusions, but should be a good method in most cases due to arteriosclerosis. Grafting is probably the only satisfactory method in obliterative arteritis, in traumatic thrombosis, and where the block is extremely long. Time and experience, however, may well modify these views. Murray did a successful modified endarterectomy in a case where syphilitic aortitis had obliterated all four great vessels.[13] In another similar patient Bahnson inserted a by-pass graft between the arch and the patent portion of the common carotid artery with immediate relief of dizziness, tinnitus, and convulsions.[12] Denman, Ehnie, and Duty have used arterial grafts for insidious thrombotic occlusion of the cervical carotid arteries.[6] Davis, Grove, and Julian have treated a case of thrombotic occlusion of the branches of the aortic arch by grafting.[4] DeBakey and Crawford have reported resection and homograft replacement of the innominate and carotid arteries and have described a shunt to maintain circulation.[5] From such case reports it appears clear that considerable benefit may be derived from arterial reconstruction or replacement.

SUMMARY

Partial or complete occlusion of aortic arch branches has commonly been considered a single entity though readily subdivided into more than three distinct types. The classical variety, an idiopathic arteritis, occurs in young women. Arteriosclerosis obliterans may cause clinically quite similar occlusions. Trauma such as pressure from a cervical rib may also cause occlusion. Embolus, aneurysm, dissecting aneurysm, syphilis, Buerger's disease, and neoplasm may be causative occasionally.

Symptoms of chronic carotid occlusion include syncopal attacks, hemiplegia, mental deterioration and visual loss. Chronic subclavian occlusion may cause shoulder or arm pain, decreased work tolerance, atrophy and gangrene.

Four case studies are presented. A young woman with classical "pulseless disease" survived ventricular fibrillation, brought on by cardiac catheterization. A man with angina-like shoulder and arm pain was shown by arteriography to have left subclavian occlusion. A woman of 36, clinically thought to have coarctation, proved to have arteriosclerotic occlusion of the left subclavian artery and the abdominal aorta. An endarterectomy of the first portion of the subclavian artery and excision and grafting of the abdominal aorta were done. A man with asymptomatic right subclavian and partial right carotid artery occlusion due to atherosclerosis has been followed but has had no treatment.

It is felt that selected cases of chronic carotid and subclavian occlusion should be treated by endarterectomy or grafting and that definitive studies of this group should therefore be undertaken whenever possible.

RESUMEN

Aunque en realidad la oclusión parcial o completa de las ramas del arco aórtico se subdividen en más de tres tipos, generalmente se han considerado como una entidad única. La variedad clásica, un arteritis idiopática, se observa en las mujeres jóvenes.

La arterioesclerosis obliterante puede causar clínicamente oclusiones similares. También el trauma, tal como la compresión ejercida por una costilla cervical, puede causar la oclusión. Ocasionalmente la causa puede ser la embolia, el aneurisma, el aneurisma disecante, la sífilis, la enfermedad de Buerger y las neoplasias.

Los síntomas de la oclusión carotídea incluyen: ataques sincopales, hemiplegia, deterioro mental, y pérdida de la vista. La oclusión crónica de la subclavia puede causar dolor del hombre o del brazo, disminución de la tolerancia al trabajo, atrofia y gangrena.

Se presentan cuatro casos. Una enfermedad con la clásica "enfermedad de la falta de pulso" (asfigmia crónica) sobrevivió a la fibrilación auricular provocada por la cateterización cardiaca.

Un hombre con dolor anginoide en el hombre y en el brazo, se encontró que tenía, según lo demostró la arteriografía, una oclusión de la subclavia izquierda. Una mujer de 36 años que se creyó según la clínica que tenía coartación, se demonstró que tenía oclusión arterioesclerosa de la subclavia izquierda y de la aorta abdominal.

La endarterectomía de la primera porción de la subclavia izquierda, y la excisión e injerto de la aorta abdominal se hicieron. Un hombre con oclusión asintomática de la subclavia derecha y oclusión parcial de la carótica derecha debida a arterioesclerosis, se pudo observar pero se trató.

Se considera que casos escogidos de oclusión carotídea crónica así como de oclusión de subclavia se deben tratar por endarterectomía o injerto y que deben hacerse estudios bien demonstrativos antes de emprenderse estos procedimientos, cuando sea posible.

RESUME

L'occlusion partielle ou complète des branches de la crosse aortique a été généralement considérée comme une seule entité, bien qu'elle ait été subdivisée en plus de trois types distincts. La variété classique d'artérite idiopathique, survient chez les jeunes femmes. L'artériosclérose oblitérante peut provoquer cliniquement des occlusions

assez semblables. Une blessure, telle que la compression d'une côte cervicale, peut également provoquer l'occlusion. L'embolie, l'anévrysme, l'anévrysme disséquant, la syphilis, la maladie de Buerger, et la néoplasie peuvent être éventuellement des facteurs déclenchants.

Les symptômes de l'occlusion chronique de la carotide comprennent les attaques syncopales, l'hémiplégie, les troubles mentaux, et la perte de la vue. L'occlusion chronique de la sous-clavière peut provoquer une douleur du bras ou de l'épaule, une fatigabilité au travail, l'atrophie et la gangrène.

Les auteurs présentent quatre cas. Une jeune femme, atteinte de la classique "affection sans pouls" survécut à une fibrillation ventriculaire, provoquée par le cathétérisme cardiaque. Un homme atteint d'une douleur de l'épaule et du bras évocatrice de l'angine de poitrine se révéla par l'artériographie être atteint d'une occlusion de l'artère sous-clavière gauche. Une femme de 36 ans, qu'on pensait atteinte cliniquement d'une coarctation, fit la preuve d'une occlusion athéromateuse de l'artère sous-clavière gauche et de l'aorte abdominale. Une endartérectomie de la première partie de l'artère sous-clavière, l'exérèse et une greffe de l'aorte abdominale furent pratiquées. Un homme atteint d'occlusion de l'artère sous-clavière droite asymptomatique et d'occlusion partielle de la carotide droite imputables à l'artériosclérose fut suivi mais ne reçut aucun traitement.

L'auteur pense que des cas choisis d'occlusion chronique de la carotide et de l'artère sous-clavière devraient être traités par l'endartérectomie et la greffe, et que des études précises sur ce groupe devraient ensuite être poursuivies dans la mesure du possible.

ZUSAMMENFASSUNG

Der partielle oder komplette Verschluss von Aesten des Aortenbogens wurde für gewöhnlich als Einheit angesehen, obwohl man sie leicht in mehr als drei voneinander verschiedene Typen aufteilen kann. Die klassische Variante, eine idiopathische Arteriitis, kommt bei jungen Frauen vor. Eine obliterierende Arteriosklerose kann zu einem klinisch ganz ähnlichen Verschluss führen. Ein Trauma, wie etwa der Druck einer Halsrippe, kann ebenfalls einen Verschluss bewirken. Embolie, Aneurisma und Aneurisma dissecans, Lues, Bürgersche Krankheit und Neoplasmen können gelegentlich ursächlich in Betracht kommen.

Symptome eines chronischen carotiden Verschlusses schliessen Ohnmachtsanfälle, Hemiplegien, eine sich verschlechternde seelische Verfassung und Verlust des Sehvermögens ein. Ein chronischer Verschluss der art. subclavia kann Schulter- oder Armschmerz bewirken, eine herabgesetzte Arbeitsfähigkeit, Atrophie und Gangrän.

Vier Fäle werden vorgestellt: eine junge Frau mit der klassischen "pulslosen Krankheit" überstand ein Kammerflimmern, das bei einer Herzkatheterisierung aufgetreten war. Von einem Mann mit Angina-ähnlichen Schulter- und Armschmerzen konnte durch die Arteriographie gezeigt werden, dass ein Verschluss der linken art. subclavia vorlag. Bei einer Frau von 36 Jahren, bei der man klinisch an eine Stenose gedacht hatte, erwies sich, dass ein arteriosklerotischer Verschluss der linken art. subclavia und der Bauchaorta vorlag; es wurde eine Endarteriektomie des 1. Teiles der art. subclavia vorgenommen und eine Exzision und Transplantation der Bauchaorta. Ein Mann mit erscheinungsfreiem Verschluss der rechten art. subclavia und einem Teilverschluss der rechten art. carotis infolge Arteriosklerose stand unter Beobachtung, wurde aber nicht behandelt.

Es wird die Auffassung vertreten, dass ein chronischer Verschluss der art. carotis und art. subclavia mit Endarteriektomie oder Transplantation behandelt werden sollte, und dass daher genau festgelegte Untersuchungen deiser Krankheitsgruppe—wenn irgend möglich—vorgenommen werden müssen.

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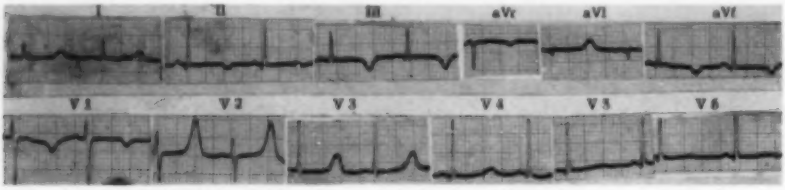
ELECTROCARDIOGRAM OF THE MONTH

Electrocardiographic Diagnosis of Idiopathic Hypoparathyroidism

A 35 year old white man was seen complaining of convulsive seizures which had been present for approximately two months, and which had consisted of about three major convulsive episodes, together with many minor abortive ones. He had also noted diminution of vision, weakness, cramping of the legs, and his wife volunteered the thought that he had undergone a personality change for the past eighteen months, so that he now seemed a good deal more lethargic than he had been. He had recently been hospitalized by a neurosurgeon, and following neurologic study, the only suspicious finding was a borderline electroencephalographic tracing; a diagnosis of idiopathic epilepsy had been made, and therapy instituted with Dilantin sodium and with phenobarbital, but these had been unavailing.



Physical examination disclosed bilateral lens opacities, and was otherwise not remarkable; routine laboratory survey was normal. The electrocardiogram (illustrated) disclosed sinus mechanism with normal conduction in a vertical heart, evidence of inferior and lateral wall ischemia, and marked prolongation of the Q-T interval with preservation of the isoelectricity of the S-T segment, and preservation of a straight segment. The Q-T interval in this tracing measures 0.56 seconds; the mean interval for this rate (Ashman) in men is 0.35 seconds, with the upper limit of normal 0.38 seconds.

Estimation of the serum calcium gave a value of 3.5 mgm. per cent, and the phosphorous level was 8 mgm. per cent. The diagnosis was hypoparathyroidism, idiopathic, and, following therapy with Hytakerol and calcium, the seizures disappeared.

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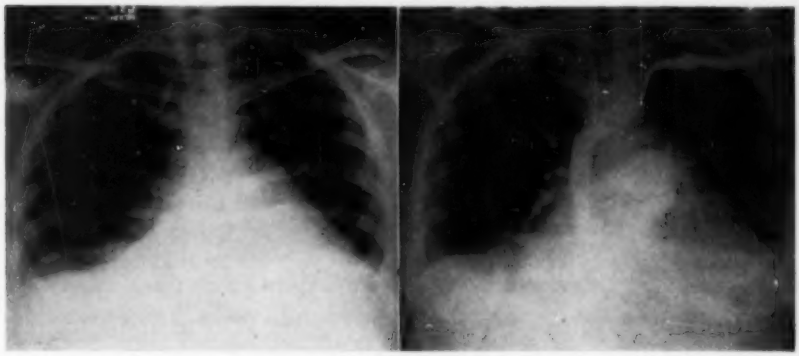
The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

X-RAY FILM OF THE MONTH

Clinical Information

The patient was a 27-year-old white woman with a two week history of anorexia, nausea, and a sensation of tenderness and fullness in her epigastrium. Her liver was enlarged and tender. Liver function tests were normal. Other laboratory studies and physical examination were negative.



Diagnosis—Pericardial Effusion

The heart is enlarged transversely to the left and right (Fig. 1). On fluoroscopy cardiac pulsations were present but diminished. The heart appears diffusely enlarged without evidence of specific chamber enlargement. The lung fields show no congestion, but there is fluid in both pleural bases. On the angiocardiogram (Fig. 2) the opacified right atrium is separated from the right "heart" margin by four centimeters. The pulmonary artery segment forms no portion of the left border, and the distance between this segment and the left border of the cardio-pericardial shadow is increased.

Pericardial effusion, more common than one usually suspects, may present no typical clinical finding. A posterior-anterior x-ray film of the chest often reveals transverse enlargement of the heart which may assume a globular or "leather bottle" contour. There may be an increased acuity of the right cardiophrenic angle which changes as the patient moves from the upright to the supine position due to the fluid gravitating to the base of the heart. The lung fields seldom show congestion. On fluoroscopy cardiac pulsations may be normal, diminished or absent, often depending on the rate of accumulation of the fluid.

In questionable cases, such as the present one, angiocardiography may be diagnostic. Opacification of the cardiac chambers establishes their size. From this, estimation of the size of the walls of the chambers may be made. Normally the wall of the right atrium measures 1 to 3 mm., the right ventricle 3 to 5 mm., and the left ventricle 10 mm. Hypertrophied ventricles rarely exceed 20 mm. in thickness. Accordingly, a soft tissue density greater than the above, especially if it surrounds the opacified chambers of the heart in the frontal view, indicates the presence of pericardial fluid.

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Case Report Section

Infection of Pneumonectomy Space with Aspergillus Fumigatus Treated by "Nystatin"

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Pulmonary aspergillosis may occur either as a primary or secondary infection.

Primary infection is rare and occurs in people dealing with grain contaminated by fungus, e.g. agricultural workers, and in people handling pigeons and parrots.

Secondary infection *may* occur as a superimposed infection on the abnormal pulmonary condition, e.g. bronchial carcinoma, pneumoconiosis, tuberculosis or bronchial fistula. It also may develop during antibiotic therapy which inhibits bacteria and promotes growth of other organisms.

Case I. A man, aged 57, a cooper and a keen amateur gardener, was admitted to this hospital in February 1957 for investigation with a presumptive diagnosis of carcinoma of the right bronchus.

Family history did not reveal anything important and he had never been seriously ill.

History of present illness consisted of intermittent pain of five weeks duration. His doctor found a marked degree of clubbing of the fingers. X-ray film revealed a round density in mid zone of the right lung.

On admission his general condition was good, he was afebrile; and complained of pain in the right chest and dry cough. His appetite was good but he had lost some weight in the past three weeks. He used to smoke 20-30 cigarettes daily, but gave up smoking five years ago.

His chest was emphysematous with a persistent rhonchus in the right mid zone. There was marked clubbing of the fingers. Apart from this there were no other signs of disease in his chest or in the other systems.

X-ray film showed a rounded opacity in the mid zone of the right lung.

His hemoglobin was 104 per cent. The white cell count was 9,450 with the following differential

Neutrophils	77	Monocytes	6
Stabs	7	Eosinophils	2
Lymphocytes	7	Basophils	1

The urine was negative.

Bronchoscopy revealed the right middle lobe orifice open. Mucous was aspirated. The carina between the two branches of the middle lobe appeared to be oedematous and biopsy showed a bronchial mucosa with only mild oedema and mild chronic inflammatory cellular infiltration. The bronchial aspirate was not contributory.

Right pneumonectomy was performed and a hard neoplastic mass involving the lower lobe with a small amount of free bloody fluid in the pleural cavity was found. Smears from pleural fluid were negative for pathogenic organism on direct examination and culture.

As a cover for operation he was given crystalline penicillin 800,000 units daily for 15 days.

On the 15th day after operation a routine blood count showed 14,300 white cells, following which his pneumonectomy space was aspirated. Culture showed Staphylococcus aureus which was resistant to penicillin but sensitive to erythromycin and tetracycline. Penicillin injections were discontinued, and a course of 500 mgms. achromycin, by mouth, was commenced, six hourly for the first three days and eight hourly for the other three days. Simultaneously he was aspirated daily, and on each occasion 1 ounce of blood stained fluid was removed from the space, and 500 mgms. of achromycin in 20 ccs. of water was inserted. Cultures of the fifth and sixth aspirations were sterile for bacteria, but the latter showed infection was Aspergillus fumigatus for the first time.

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The course of achromycin was discontinued, and treatment with a solution of brilliant green was started.

Following this he was aspirated for the following six days, and about four to eight ounces removed on each occasion. On the first three days 25, 40 and 60, and on the last three days 100 ccs. of solution of brilliant green in strength 8/1,000,000 was inserted into the space.

At the end of this treatment, however, cultures of fluid still showed Aspergillus fumigatus, and this treatment was discontinued. He was then aspirated daily for the next 21 days, and a suspension of Nystatin, 450 ccs. in strength 100 units per ml., were inserted into the space during the first week, and during the remaining 14 days 700-800 ccs. of Nystatin, 500 units per ml., were used.

The amount of fluid aspirated from the chest varied from 450 to 800 cubic centimeters, depending largely on the amount of suspension of Nystatin used on the previous day.

At the beginning of this treatment the culture showed a moderate growth as Aspergillus fumigatus, and at the end of the first week there were three to eight colonies seen; during the second week cultures of fluid were intermittently positive, and during the third week they became, and remained, steriie.

After obtaining seven consecutive negative cultures for Aspergillus fumigatus. and being symptom free, with a normal blood count, he was discharged. He is now well and working.

Case II. A 43 year old roadman, was admitted to this hospital in April 1957, with a collapsed right middle lobe, for investigation and treatment.

His family history did not reveal anything important.

He had never been seriously ill.

His present illness consisted of fever of eight weeks duration followed by productive cough with yellowish sputum stained with blood on a few occasions; pain in the right chest; dyspnoea on exertion; with a loss of half a stone in weight in the past six months.

On admission his general condition was fair; he had a slightly raised temperature; he complained of cough with a half cupful of yellowish sputum in 24 hours; pain in the right chest, and dyspnoea on exertion. He had smoked 20 cigarettes daily since youth.

There was impairment of respiratory movements on the right and dullness in the right middle zone anteriorly with *no* adventitious sound. Mild clubbing of the fingers was present. Nothing abnormal was discovered in the other systems.

A chest x-ray film showed the right middle lobe collapsed. The hemoglobin was 98 per cent. There were 15,000 white blood cells as follows: Neutrophils 52, Stabs 13, Lymphocytes 22, Monocytes 11, Eosinophils 1, Basophils 1.

Bronchoscopy showed pus in the right main bronchus coming from the middle lobe orifice which was aspirated. The lips of the middle lobe orifice were oedematous and narrowed. Biopsy revealed squamous carcinoma.

Right pneumonectomy was performed, and on the fourth day his temperature was 100°F, and white blood cell count 17,100. Cultures of pleural fluid from the space were sterile for bacteria, but showed infection by Aspergillus fumigatus.

As cover for operation he was having 800,000 units of crystaline penicillin daily.

Penicillin injections were discontinued and he was aspirated daily for the following 10 days, when between 6 and 10 ounces of thin blood stained fluid was removed each time and replaced with the same amount of suspension of nystatin in strength 500 units per ml.

After three days of this treatment cultures became, and remained, sterile.

He was discharged after obtaining seven consecutive cultures negative for this infection. He is now well and symptom free, with normal blood count.

DISCUSSION

In the treatment of pulmonary asperigillosis various drugs, such as iodides and neoarsphenamine, (2) hydroxystillbamadine, are recommended, but results are unsatisfactory.

According to Hinson et al (1952)[1] iodides and neoarsphenamine were of no value in the treatment of his cases, however, Aspergillus fumigatus was inhibited in vitro by M and B 938 in concentration of 1: 100,000. Seabury (1956)[2] treated a case of aspergillosis of an orbit associated with pulmonary lesions with 2-hydroxystillbamadine without effect.

Riddell (1956)[3] says that "inhalation of 'nystatin' in suspension, or of solutions of brilliant green, or hydroxystillbamadine is effective in suppressing or removing Aspergillus fumigatus from the bronchial secretions."

In the above mentioned cases of infection of the pneumonectomy space with Aspergillus fumigatus an aqueous suspension of Mycostatin, consisting of 100 and 500 units per ml. was used. The suspensions were prepared daily and none was older than 48 hours. Mycostatin sterile powder was obtained from Messrs. E. R. Squibb & Sons, New York.

The first patient had 21 daily aspirations and instillation of a suspension of Nystatin; during the first seven days 400 ccs. of fluid, in strength 100 units per ml., and during the remaining 14 days 700-800 ccs. of strength 500 units per ml. was used.

The second patient has 10 daily aspirations and replacements with the same amount of suspension of Nystatin of 500 units per ml. The amount used on each occasion was between 180 and 280 ccs.

No Nystatin was given by mouth, and while they were having instillations of Nystatin into the chest no other antibiotics were used. No toxic symptom was observed during this treatment.

During this course of treatment with Nystatin wet smear and cultures were gradually improving, and after obtaining seven negative cultures on consecutive days both patients were discharged. Both patients were seen in March 1958; both are well and symptom free and doing full-time work.

In the first case the infection of the pneumonectomy space was most likely due to antibiotic therapy, and in the second case the infection could have developed from the bronchial stump or through a small bronchial leak or space becoming infected by Aspergillus fumigatus during operation.

ACKNOWLEDGMENT

My thanks are due to Mr. Christopher Parish, Chest Consultant in Cambridge, for his valuable help; to Dr. D. Barron Cruickshank, Pathologist, and Mr. Boot, Senior Technician, Sims Woodhead Memorial Laboratory, Papworth, for laboratory investigations connected with this paper; to Colonel G. C. Bess and Major Joseph Ford of the U.S.A.F. Hospital at Wimpole Park, for their valuable help in material provided at short notice.

Addendum: Both patients who were seen in March, 1959 are fit and well.

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Mediastinal and Subcutaneous Emphysema, Pneumothorax, Pneumoperitoneum and Myocardial Infarction Occurring Simultaneously*

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A Case Report

Mediastinal emphysema is commonly followed by or associated with pneumothorax and may be complicated by the development of subcutaneous emphysema, retroperitoneal emphysema and pneumoperitoneum. Because of similarities in the clinical pictures of pneumothorax, mediastinal emphysema and myocardial infarction the following case, combining all these entities simultaneously, is reported.

A 93 year old woman (C. G. H. No. 22063) was brought to the hospital on November 4, 1956 in an unconscious state after having collapsed in church. From her son it was learned that she had suffered from breathlessness and chest pain on exertion, and had had swelling of the feet and legs.

Examination revealed a thin, pale woman with cold, clammy skin, slow but regular respirations, and no detectable blood pressure or heart sounds. On cursory examination the chest and abdomen were unremarkable and no paralyses were noted. With administration of nor-epinephrine the systolic pressure rose to 80 mm. Hg. Shortly afterwards she began to vomit.

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Ninety minutes later the blood pressure was 110/65, the pulse 40, respirations 35 and temperature 98°F. She was quite alert. For the first time marked subcutaneous emphysema of the chest wall was noted, making evaluation of breath sounds difficult. The abdomen had become tense, distended and tympanitic. Neither edema nor cyanosis were detected. Peripheral pulses were present.

At this time a chest roentgenogram showed left ventricular enlargement, fractured ribs and pneumothorax on the left, air within the mediastinum, marked subcutaneous emphysema, and air beneath the diaphragm (Fig. 1). Two thousand ml. of air were aspirated from the left chest and a No. 20 polyethylene catheter was inserted and connected to water-seal drainage. Three days later she pulled out the tube as well as a venous cutdown. Within five days of admission radiographic evidence of pneumothorax had disappeared.

The initial electrocardiogram on November 4, 1956 was interpreted as showing complete A-V block and acute posterior myocardial infarction with possible septal involvement (Fig. 2). On November 6, 1956 there was a varying degree of A-V block and evidence of acute postero-septal infarction (Fig. 2). On November 9, 1956 first degree A-V block was present and on December 4, 1956, sinus rhythm and evolving acute postero-septal myocardial infarction.

On admission the white blood cell count was 22,400 with a marked left shift; two weeks later the count was still 12,000 with 72 per cent neutrophils. Maximum sedimentation rate recorded was 31 mm./hr. Urine contained one-plus albumin and the nonprotein nitrogen was 68 mgs./100 ml.

Treatment consisted of vasopressors and oxygen initially, bedrest, and anticoagulation for one month. Her temperature remained between 100-101°F. for 11 days, then returned to normal. She appeared to improve steadily and was discharged one month after admission.

One month later she experienced severe chest pain and was admitted to Denver General Hospital where she died within one and one half hours. At post-mortem examination both pleural spaces contained several hundred ml. of clear, yellow fluid. The heart weighed 350 gms.; throughout the posterior portion of the septum and the postero-lateral wall of the left ventricle firm, gray fibrous tissue partly replaced the myocardium. The coronary arteries all had pinpoint lumina, but no occlusion was

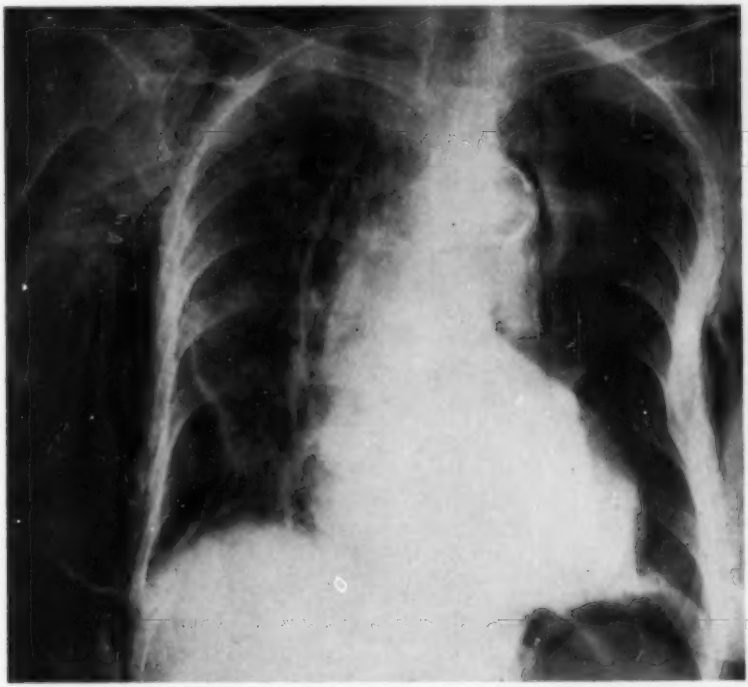

FIGURE 1: Upright chest roentgenogram taken November 4, 1956, showing fractured ribs and pneumothorax on the left, mediastinal and subcutaneous emphysema, air beneath the diaphragm and cardiac enlargement.

demonstrable. The lungs were congested. On microscopic examination, only a few myocardial fibres remained in the posterior wall of the left ventricle, being replaced by loose fibroelastic tissue.

COMMENT

It seems probable that the fractured ribs (however they were sustained) or trauma related to their production injured the left lung, causing rupture of alveoli in continuity with perivascular sheaths, development of pulmonary interstitial emphysema and subsequent mediastinal emphysema. Pneumothorax, subcutaneous emphysema and pneumoperitoneum could have ensued and the effects of some of these processes could have contributed to the occurrence of myocardial infarction. Alternatively, myocardial infarction may have initiated the train of events, causing the woman to fall or slump over, injuring the chest and producing lung trauma.

The pathogenesis of pulmonary interstitial emphysema and mediastinal emphysema was described as long ago as 1888 by Müller[1] and more recently by the Macklins.[2] Air from ruptured alveoli may reach the hilum (and then the mediastinum) by dissecting its way along perivascular spaces in the lungs. Mediastinal air can accumulate to such an extent as to compress the pulmonary veins and impede the return

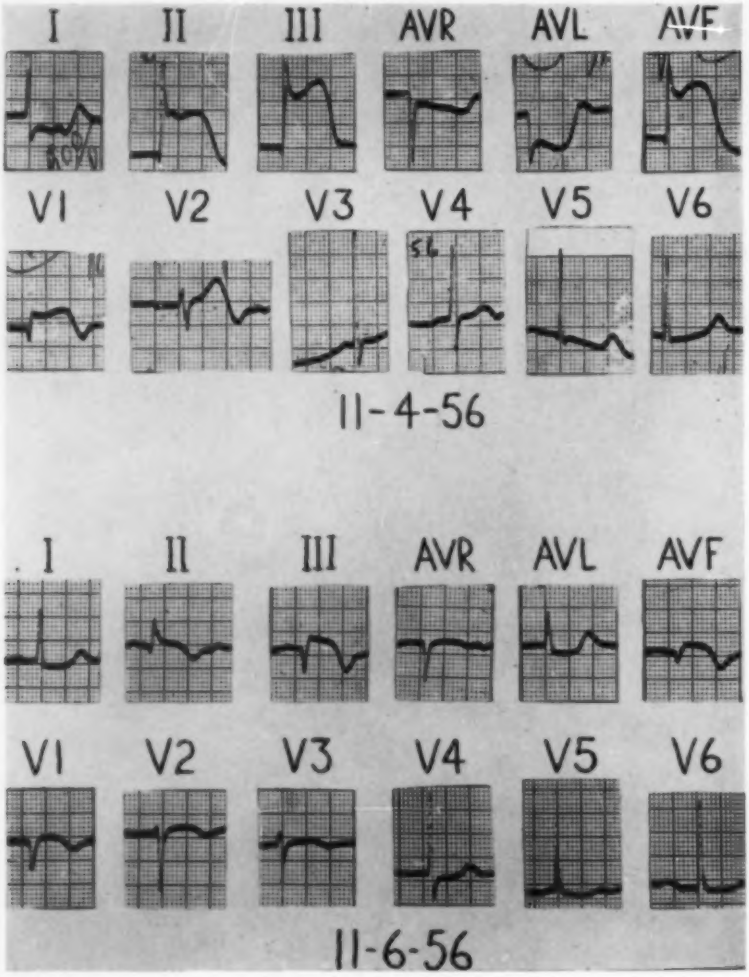

FIGURE 2: Electrocardiogram on November 4, 1956 and November 6, 1956, showing acute posteroseptal myocardial infarction. Complete heart block was present on November 4 and varying A-V block on November 6, 1956.

of blood to the left atrium (the so-called "air block").[3] Experimentally, elevated pressure within the mediastinum is followed by hypotension, dyspnea, cyanosis and venous hypertension.[3] Mediastinal air can rupture into either pleural space or may escape into the tissues of the neck, face, floor of the mouth, axilla, anterior chest wall and arms, or dissect downward along the esophagus or aorta to enter the retroperitoneal space[4] from where it may rupture, causing pneumoperitoneum. The "escape" of air into subcutaneous tissues may be life-saving.[5] Since both pneumothorax and pneumomediastinum have been described as complications of artificial pneumoperitoneum[6, 7] it appears that adequate communications, including the esophageal and aortic hiatuses, as well as congenital defects, exist between the peritoneal space and the thorax.

The signs and symptoms of spontaneous pneumothorax and mediastinal emphysema are well known.[8, 9] Chest pain is almost always present and may radiate to the back, shoulders, neck or arms. It is likely to be aggravated by cough, and in the case of mediastinal emphysema, by swallowing. Dyspnea is more common in pneumothorax and may be associated with cyanosis, pallor, sweating, tachycardia and hypotension. The pain of these conditions may closely simulate that of myocardial infarction, pericarditis, dissecting aortic aneurysm, pulmonary embolism, mediastinitis or ruptured abdominal viscus. Mediastinal "air block," causing impairment of coronary circulation, has been suggested as one mode of origin of pain in mediastinal emphysema; distention of mediastinal tissues alone seems a satisfactory explanation for the pain.[10] Careful examination of the chest combined with roentgenography and electrocardiography should allow differentiation between the above conditions.

The electrocardiogram in mediastinal emphysema is not distinctive; in pneumothorax nonspecific changes in T waves and ST segments may occur, especially if the subject is supine, thus allowing air to interpose itself between the heart and the anterior chest wall.[11] The temperature curve, sedimentation rate and white blood cell count remain normal in uncomplicated pneumothorax or mediastinal emphysema.[12]

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Tietze's Syndrome: A Case Report

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In 1921 Tietze reported four cases of a syndrome of unknown etiology characterized by the appearance of painful swelling in the area of the upper chest cartilages. The clinical course is prolonged, benign, and usually only moderately painful, although at times incapacitating from severe pain. Since Tietze's original description approximately 159 cases have been reported in the world literature and, of these, only 24 have been submitted to biopsy. Although relatively few cases have been reported, many patients with acute chest pain due to this syndrome may go unrecognized and thus the problem may not be so rare. The following is a case report which required surgery, and another histopathological specimen has become available.

A 33 year old white married woman was admitted to St. Vincent's Hospital on September 15, 1957 because of severe right anterior chest pain of 12 hours duration. She had been well until September 6, 1957 when she had an acute episode of malaise and temperature to 103° F. Within 24 hours the fever subsided not to return, but dull pain in the right thorax and right shoulder developed, exacerbated by respirations and motion. Repeat physical examinations and chest fluoroscopy as well as a gall bladder series were unrevealing. Some relief was afforded with 'meprolone'-2 administered four times daily for four days, but on September 12, 1957, six days after the onset of the illness, the pain became exquisite. The pain now was localized to the area over the right third costal cartilage and a discernible swelling was present at the same site.

Physical examination was unremarkable except for a warm, extremely painful swelling over the right third costal cartilage.

Laboratory data: white blood cells 8,200 normal differential, hemoglobin 14.3 grams per cent, sed rate 14 mm/hour, C reactive protein negative, total protein 6.8 grams per cent, albumin 5 grams per cent, globulin 1.8 grams per cent, alkaline phosphatase 4 Bodansky units, blood urea nitrogen 9, fasting blood sugar 80. X-ray film examination of chest, ribs, thoracic spine and skull were entirely normal. Electrocardiogram was normal.

She remained afebrile in the hospital though in extreme pain. No benefit was noted from prednisone, 60 mgm. a day, for five days. Some relief was obtained with repeated intercostal xylocaine nerve blocks. Observation was continued at home. She received narcotics and a one week course of 'butizolidin' 400 mgms. daily without improvement. On October 26 the swollen area became more painful with associated ecchymoses of the skin. Although the clinical picture was consistent with Tietze's syndrome, she was rehospitalized for surgical resection of the involved cartilage because of the protracted incapacitating pain.

At surgery incision revealed subcutaneous edema and ecchymoses of the tissues in the area. The pectoral muscle was edematous. The third right costal cartilage was found to be buckled forward at an acute angle

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just medial to the costochondral junction. The right third rib and costal cartilage were resected from lateral to the costochrondeal junction to the sternum leaving the periostium and perichondrium on the posterior aspect in situ. Postoperatively the patient was relieved of all pain and has had no recurrence.

Histopathological examination by Dr. Arthur Ginzler revealed normal hematopoietic marrow. The cartilage was totally unremarkable.[3, 4] Small fragments of fat tissue were variable infiltrated with lymphocytes and mononuclear cells; the latter were characterized by usually large irregular coarsely hyperchromatic nuclei and basophilic cytoplasm.

DISCUSSION

The etiology and pathogenesis of Tietze's syndrome remain unknown. The onset may be fever, as has been described by other authors, suggesting and ill defined general system reaction to as yet undisclosed agent. The therapy of this condition usually requires only mild analgesia. However in this case, full doses of two antiphlogistic agents, prednisone and "butizolidin" were also tried and found to be ineffective. This necessitated surgery with excellent results.

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Editorial

Management of Recent Tuberculin Converters

It has been encouraging to note that over the past two years the attitude concerning the use of antituberculosis therapy in the newly infected child has changed from uncertainty to affirmative. Several factors seem to have influenced this change. The knowledge that INH does prevent the spread of tuberculosis from a demonstrated primary lesion to other parts of the body and the recent sharp decrease in the cases of meningeal and miliary tuberculosis and other evidences of generalized infection in treated children have provided the assurance of effectiveness in using INH at the earliest possible time.

The more general acceptance of the fact that a converted tuberculin test is indication of an active tuberculous process in that body even though it cannot yet be demonstrated by roentgenograms or supported by physical signs or symptoms tends to justify the initiation of antimicrobial therapy at the earliest and most effective time. The progressively increasing proportion of young children who respond negatively to the tuberculin test has tended to direct more urgent attention to those which are positive, especially to those which have recently converted. This has promoted the possibility of preventing serious clinical tuberculosis. The fact that BCG vaccination has not been generally accepted as an effective preventive for tuberculosis has served to emphasize the importance of using drug therapy at the earliest possible time with the expectation of thwarting the beginning tuberculous lesion.

The lack of decline in the incidence of tuberculosis has emphasized the need for caution against placing dependence on the therapy of advanced cases for the control of tuberculosis. These factors along with the knowledge that the antimicrobials are more frequently becoming useless by reason of bacillary resistance or toxicity prompt us to place greater and greater emphasis on the preventive or at least early treatment possibilities in tuberculosis control. In this light prevention and early treatment must be considered not only from the standpoint of the beginning tuberculosis in the recent converter but also of the adult whose endogenous reinfection can occur only from a poorly healed primary tuberculosis. Antimicrobial therapy has boomeranged in the form of the persistently positive highly resistant patient who is recalcitrant and despite laws passed for his control continues to menace his relatives and others with his infection. Until this type of patient is brought under control the need for diligence in detecting and protecting the newly infected child is still an extremely important part of the tuberculosis control plan.

At the New York annual meeting and again in the Philadelphia Interim Session of the American College of Chest Physicians much discussion was given to the matter of managing the case of the recent converter. There are some who do not agree that *all* cases of recent tuberculin conversion require antimicrobial therapy. They argue that most children can handle a mild tuberculous infection very well without specific therapy, that antimicrobial therapy given too early serves to suppress the acquisition of

additional resistance to the invading organisms and that withholding it until a definite tuberculous lesion can be demonstrated still provides adequate control of the situation.

There are others who require specific indications for the use of antimicrobials in the recently infected child; these indications range from (1) demonstration of a primary lesion, (2) clinical evidence of an active tuberculous process, (3) violently positive tuberculin reaction, (4) evidence of a virulent infection as indicated by the progressive type of tuberculosis in the source case or even (5) to familial tendencies which would prompt the use of therapy in any of its members. Unless one or some of these indications are present they would not justify the use of antimicrobial therapy in the recent converter.

Either approach is reasonably sound. But the matter cannot be resolved by making the decision to treat or not to treat the recent converter either in the light of special indications or just on general principles. The recent converter represents a new case of active tuberculosis which may show rapid progression to demonstrable, clinical tuberculosis or may not. But the case which does not provide indications for immediate therapy must not be disregarded; it must still be considered as a potential case of active tuberculosis and watched closely for any signs of that condition. The finding of no positive signs at the initial examination, other than the converted tuberculin test, must not permit a false sense of security. Delaying the next examination for the usual three to six months may very well result in the development of serious, progressive tuberculosis before the next "routine" recheck examination.

In our experience at Maybury Sanatorium many of the severely ill children came from non-tuberculosis clinics or general hospitals having been treated for a mis-diagnosed pulmonary illness after having previously been known as a tuberculosis infected case. The recently infected child must be re-examined every four to six weeks routinely and upon the presentation of any sign or symptom. The mother or another responsible member of the family must be aware of the situation and be alert to any evidence of progressive tuberculosis and must take the child to the tuberculosis clinic or the doctor who is aware of the diagnosis.

The infected child in which roentgenological examination is reported as negative must not be assumed to be in a secure position because it is well known that it is very difficult to get a good chest film on a frightened young child and that even in good films the early primary lesions may be hidden or not identifiable. We must not be content with negative findings too early. Progressive tuberculosis may occur several months or even years after conversion of the tuberculin test. The child with a recent tuberculous infection may be successful in avoiding serious clinical tuberculosis from that first dose of tubercle bacilli but he may be quite unsuccessful with subsequent multiple infections. The source of contact must be uncovered and the child protected from further infection. In our experience 68 per cent of the contacts were members of the family but another 21 per cent were non-relatives variously associated with the home—only 15 per cent were previously known cases of tuberculosis. Thus in searching for the source of contact one must be diligent and resourceful if the infected child is to be protected from further contact. When the

source of contact has been identified and an infection suspected it must be kept in mind that there is an incubation period in which the tuberculin test will not yet have become positive. It is well to remember also that in a very sick child there may be an anergic state in which the tuberculin test will not be positive. Failure to recognize either of these possibilities may lead to serious misdiagnosis and mishandling of a case.

The tuberculin test must be made a part of the routine examination of all young children; to wait for the usual tuberculin surveys in the schools will result in missing the opportune time to introduce antimicrobial therapy or other control measures in many an infected child. Our experience shows that 75 per cent of the children at Maybury were infected and had the onset of illness before they reached school age.

At the Fireside Conference in Philadelphia it was the agreement of the majority that (1) with few exceptions, the recently converted tuberculin case should be given isoniazid in doses of about 5 to 3 mg./Kg./day (some felt that PAS should also be given) and continued for a year; (2) the older the child past three years, the smaller the reaction to tuberculin and the less positive the evidence of infection the less urgency is attached to initiating treatment; (3) the recent converter which is not treated must be handled as a potential case of clinical tuberculosis; (4) in addition to the immediate treatment of a recently developed case of tuberculosis there must be considered the matter of reducing or eliminating the chances of that person becoming endogenously reinfected later in life; (5) as well as managing the infected child there is importance attached to the protection of that and other children from the undetected and recalcitrant cases of tuberculosis.

I have been encouraged by the apparent increase in attention recently being given to the matter of children in relation to the control of tuberculosis. I am quite sure that the methods used in the past have fallen far short of controlling tuberculosis and that so long as we continue being content to treat advanced cases of tuberculosis in adults and children we will continue to fail. The recent discussion of the manner of handling early tuberculosis in children seem to indicate a change of interest, which when linked with the application of proved methods of prevention provides good possibilities of greater success in controlling tuberculosis in the future.

I am enthused about the effect of these discussions at our recent meetings and hope more of them will be included in future programs.

W. L. HOWARD, M.D., F.C.C.P.
Northville, Michigan

The President's Page

THE STETHOSCOPE AND SERENDIPITY

A momentous era in medicine was opened by the first physician who utilized a straight tube to investigate physiological and pathological processes he couldn't see. For a long time now, the stethoscope has been the symbol of the physician, the very embodiment of the skill which raised the sick. What is more, it has been a powerful symbol to physicians themselves. For most of us, the day we hung our first stethoscope around our neck was the day we began to *feel* like a doctor.

Hence the prospect of the physician of the future without a stethoscope is painful. For a long time young men of science have been muttering that the stethoscope required more intuition than science and their elders have lamented the appearance of a new generation which didn't know how to use the device. We have no idea about the right of the quarrel, but it is obvious that time is on the side of the young men. The stethoscope has already lost its authority; very few, probably, would support the results of a stethoscopic examination when they were contradicted by radiology. It has already been "supplemented" out of its central place in diagnosis. One must assume that it will be ultimately supplemented out of diagnosis altogether. It will probably linger on the medical scene for some time after that, acquiring the gilt and ornamentation human beings lavish on obsolete symbols (like the garish armor that was made after gunpowder had made armor a useless burden), but finally some will want to abandon altogether.

And it will be a sad day for medicine, depriving it of some of its sense of adventure even if it does not have more serious consequences. The very ambiguity of stethoscopic findings is stimulating. We freely concede that mechanical diagnosis, with or without machines, may well be more accurate. The physician whose function is to simply ask the right questions of the appropriate diagnostic devices and correlate their unambiguous answers has a very small chance of coming up with manifestly wrong diagnoses. But the very efficiency of such an approach to diagnosis—which peers at us over the medical horizon—makes for a kind of rigidity. One can't ask any questions which aren't printed on the dial, so to speak, nor get any answers which the inventors of the technique didn't foresee. The physician has no longer any possibility of finding out something new.

The wonderful thing about the stethoscope, on the other hand, is that it is an invitation to discovery. The physical examination of the patient can be a genuine exploration, in which the physician palpates around just to find out what he can find out. He doesn't have to begin with any questions at all; he just has to be alert. As a result, he is open to new questions raised by the findings themselves.

The direct contribution of the stethoscope to medical progress is impossible to calculate, but manifestly its indirect contribution has been immense. It has made serendipidists of us all, and to date at any rate serendipity, the alert curiosity which tries to correlate oddities to other oddities instead of dismissing them, has been largely responsible for the progress of medicine. It has made every physician in some sense also a researcher; we have advanced together. And if the last stethoscope is hung up the practicing physician will have surrendered responsibility for the future of medicine to others, to purely mechanical men.

Sidney Farber

Report of the Committee on Membership

Between September 1, 1958 and March 1, 1959, 269 applications from all parts of the world were received and presented to the Board of Regents. Of these applications, 92 were for Fellowship, 60 for Associate Fellowship, 45 for Associate Membership, 71 for advancement to Fellowship and 1 for advancement to Associate Fellowship. Of this group, 208 applications were filed by physicians in the United States and Canada and 61 by physicians in other countries.

Of the total of 269 applications presented to the Board of Regents, 3 were rejected, 1 advancement to Fellowship was denied and 2 applications are being held for further investigation. Of the 57 physicians in the United States and Canada who applied for Fellowship, 7 have been reclassified as Associate Fellows until they complete the Fellowship examinations. The balance of applicants for Fellowship hold certification by one of the American Boards or the Royal College of Physicians and Surgeons.

With the admission of 192 new members in all parts of the world, the total membership of the College is now 6627. As of May 15, 1959, there were 50 applications pending presentation to the Board of Regents at the Interim Session. Other applications will be filed between now and September 1.

Chevalier L. Jackson, M.D., Chairman

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CALENDAR OF EVENTS

National Meetings

Interim Session, American College of Chest Physicians
Dallas, Texas, November 29-30, 1959

26th Annual Meeting, American College of Chest Physicians
Miami Beach, Florida, June 8-12, 1960

Postgraduate Courses

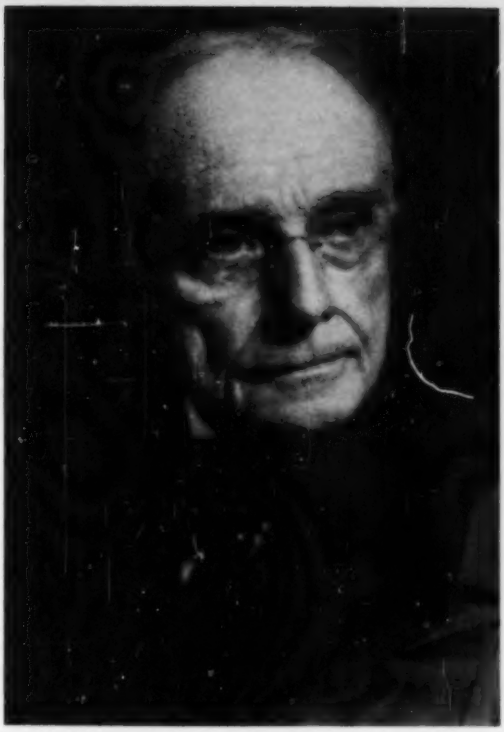
5th Annual Course on Diseases of the Chest
Los Angeles, December 7-11, 1959

13th Annual Course on Diseases of the Chest
Philadelphia, March 14-18, 1960

Chapter Meetings

Southern Chapter, Atlanta, November 15-16
Pacific Northwest Chapter, Sun Valley, January 7-9, 1960

Obituary



CHEVALIER JACKSON, M.D., Sc.D., LL.D., L.H.D., F.A.C.S.
1865 - 1958

Like a Hick'ry cog
In the old mill wheel
He did his part
As his turn came 'round.

With these words as a postscript, Chevalier Jackson closed his autobiography. He considered his life's work and responsibilities in this vein and with determination, persistence and singleness of purpose fulfilled his role in life as he saw it in spite of hardship, adversity, discouragement and even ridicule. It is gratifying to know that he lived to see his accomplishments appreciated at their full worth, and to know that many of his pioneering procedures became standard, routine techniques in both the diagnostic and therapeutic aspects of diseases of the air and food passages.

Chevalier Jackson was born in Pittsburgh, Pennsylvania on November 4, 1865. His mother and father were natives of the state. French ancestry gave him his name, and a love of the French language, the culture and the country itself throughout his life. His early years in Pittsburgh, in a coal mining and farming community were rough, but habits of early rising, long hours of work and a keen interest in drawing, painting and making things with his hands were developed at this formative stage. At twelve years of age he had had his first experience in retrieving a foreign body—tools used in drilling for oil, lost down a 1500-foot test well. The successful solution of this mechanical problem further molded his later career, the achievement of a task previously considered "impossible" continued to stimulate him throughout his life.

Early schooling was most difficult—not because of schoolwork, but because of the bullying by the larger, rough miners' boys in the country school. The study of medicine, as was customary at that time, was begun under a preceptor. In 1884 after working for a year painting glass and china to obtain funds, Dr. Jackson entered Jefferson Medical College. The medical curriculum consisted of two winter courses of lectures and clinics from October through March. At the conclusion of the first winter course he became a salesman of medical books. This took him to New England and gave him the opportunity to study his texts while waiting in doctors' offices; unfortunately, the physicians usually claimed they were too busy to read books and sales were few. Completing the coverage of his territory in Gloucester, Massachusetts, Jackson shipped on a Gloucester fishing schooner for the remainder of the summer at ten dollars a month plus a share in the catch. Taking over as ship's cook improved his income. This and his earnings from another month's work in a decorating shop painting china enabled him to return for his second year of medical school. His medical degree was conferred in 1886 when he was but 21 years of age.

Specialization in a limited field was rare at that time but interest in the field of laryngology, stimulated by the work of J. Solis Cohen and the writings of Sir Morell Mackenzie led to a trip to England to visit Mackenzie's clinic. Returning from Europe as a specialist at the age of 22, Jackson began his work in laryngology in Pittsburgh. He demonstrated the value of tonsillectomy and adenoidectomy in children and tried to establish a health program of throat inspection in the public school system. Although this effort was unsuccessful, the experience in dealing with government agencies was of value later in pressing legislation concerning the labeling of lye as poison.

His interest in endoscopy began in 1890 when he developed an esophagoscope

with which he removed a dental plate from the esophagus of an adult, and a coin from a child's esophagus. Adoption of Einhorn's suggestion of using a light carrier on the speculum made it a practical instrument, the basic design of which has been retained in most of the present day esophagoscopes. A vast experience in intubation and tracheotomy for diphtheria, and experience in the management of post-diphtheritic laryngeal stenosis acquired during the last decade of the nineteenth century, served as a background for subsequent work in bronchoscopy. Foreign body extraction proved an absorbing challenge in the years that followed. This necessitated the development of new instruments, techniques and procedures. Jackson insisted on perfecting the solution of a mechanical problem of foreign body extraction by trial, first on the manikin board, then in the cadaver and finally in the anesthetized dog. Constant research, self-training and discipline permitted him to achieve perfection, utilizing these progressive steps. Jackson stressed the principle of education of the eye and the fingers through practical experience gained by extracting foreign bodies from the air and food passages of anesthetized dogs. Physicians from every country in the world participated in the courses which he conducted in Pittsburgh, later in Philadelphia and in Paris.

In 1899 Chevalier Jackson married Alice White of Pittsburgh. She accepted and understood his devotion to the development of his special field of medicine. She encouraged him and sheltered him from what they both considered unnecessary social obligations that might take time from study or writing. She preceded him in death by only a few months.

By the turn of the century, Jackson was receiving increasing recognition in the field of laryngology and in the new fields of bronchoscopy and esophagoscopy. In 1911 he was President of the American Laryngological, Rhinological and Otological Society and in the following year was elected Professor of Laryngology at the University of Pittsburgh. However, a change in activity was necessitated at this time by an attack of pulmonary tuberculosis. Enforced rest was mandatory but the time was far from lost. Characteristically, rest periods became an opportunity to write, and the first complete text on "Peroral Endoscopy and Laryngeal Surgery" was prepared and published in 1914. This and an earlier text in 1907 were richly illustrated by Jackson who stressed this form of teaching in lectures as well as texts. No one who ever saw him sketch with both hands while lecturing will forget the drawings or the points they illustrated. He used his line and chalk drawings as well as oil paintings of endoscopic pathology in the texts and they became the basic works in this new field of medicine.

Foreign body work became Chevalier Jackson's greatest interest and his skill in the management of the difficult case and his success in safely removing a foreign body after others had failed were soon universally recognized. However, more than anyone else, he demonstrated the value of bronchoscopy and esophagoscopy in the diagnosis and treatment of other diseases of the chest, and the safety with which these procedures could be done in infants as well as adults. Peptic esophagitis, the upper and lower pinch-cock of the esophagus, bronchial adenoma, post-operative atelectasis and other phenomena he described were received with skepticism, but later were accepted as definite clinical entities. In 1916 Jackson was offered the Professorship of Laryngology at Jefferson Medical College and moved to Philadelphia to accept this position. Here he became recognized as the world's leading laryngologist and bronchoscopist. In 1917 he was instrumental in founding the American Bronchoscopic Society and served as its first president. He had been a Founder Member of the American College of Surgeons in 1913. In 1919, he was elected to fill the new chair of Bronchoscopy and Esophagoscopy created for him at the University of Pennsylvania Graduate School of Medicine. He later received similar appointments at Temple University and Woman's Medical College. He became President of the Woman's Medical College in 1935.

During these years Jackson received innumerable medical honors in this country and abroad. He traveled widely to give papers on bronchoscopy and allied subjects and visited all parts of the world to teach the principles and techniques of peroral endoscopy. He was an honorary member of medical societies throughout Europe, North, South and Central America and all parts of the United States. In 1926 he was President of the American Laryngological Society and received the DeRoaldes Award in Laryngology. He was a recipient of the Philadelphia Bok Award, was made a Chevalier de la Legion d' Honneur (France) and Chevalier de l'Orde de Leopold (Belgium) in 1927. He was the recipient of the Henry Bigelow Medal awarded by the Boston Surgical Society in 1928;

the Cresson Medal of the Franklin Institute in 1929, the I. P. Strittmatter award in 1932 and in 1933 received the Gold Medal of the Radiological Society of North America. The highest honor in American Medicine, the Distinguished Service Medal of the American Medical Association was conferred on him in 1940. The award of the American College of Chest Physicians, for meritorious Services in Diseases of the Chest, was given him in 1952.

Jackson was the first to point out that the field of peroral endoscopy had broadened to justify considering it as an "-ology" rather than an "-oscopy"; a "study of" rather than merely a "looking into." He coined the word "broncho-esophagology" to indicate this advance and it has come into common usage. Those who stumbled over its pronunciation were gently reminded of the similar term, "gastroenterology."

One of the achievements accomplished through the dogged determination so characteristic of Dr. Jackson was the passage of the Federal Caustic Act by Congress in 1927. He effected this through personal appearances before numerous senators, congressmen and committees. He used the many children under his care at that time as a living demonstration of the need for this legislation. This law made mandatory the labeling of caustics as poisons and required the printing of the antidote on the label. Jackson obtained great personal satisfaction from this triumph. The pen with which President Coolidge signed this bill was presented to him by the President.

Holding five chairs of Bronchoscopy and Esophagoscopy in as many separate medical schools was a unique achievement. It attested to Jackson's constant drive to teach and to broaden the field of bronchoscopy. In the separate clinics he developed individuals who carried on his work in strictest adherence to his principles. Dr. Ellen J. Patterson of Pittsburgh continued his work there when he moved to Philadelphia. Dr. Louis Clerf continued at Jefferson Medical School, maintaining the international reputation of that world famous clinic. Dr. Gabriel Tucker carried on in like manner at the Graduate School, as did Dr. Emily Van Loon at the Woman's Medical College.

The great modesty, sincerity and singleness of purpose of this man who lived through almost a century of medicine can hardly be realized. He developed a specialty through keen observation, consummate skill and great perseverance. He discussed its problems and their solutions with his colleagues, but his wealth of clinical experience kept him far in the lead in any consultation. He gave his opinion when it was asked, but often with the disarming statement, "But of course, I have just one vote, you know." His kindness, gentleness, and courtesy pervaded all his actions and these basic attitudes commanded the greatest respect from his patients and the colleagues who worked with him. Yet his strict formality gave only a very few an opportunity to know him except through medical discussions. Those few who had the privilege of a visit to "The Mill" where he lived in the beautiful countryside outside of Philadelphia saw a man keenly interested in nature and humble in his appreciation of the beauty of his surroundings. He was fascinated by the mechanics of the mill wheels, the electric boat he used on the mill pond and the wood and metal tools he could use so well. Even carving a roast at dinner was a task requiring a host of instruments, all laid out before him with precision and in exact order. At Old Sunrise Mills he cherished the warmth of the family circle. He derived great pleasure, for example, working with his granddaughter preparing the drawings for one of his last papers, illustrating the types and action of grassheads as foreign bodies in the bronchi.

Dr. Jackson experienced great personal satisfaction in the establishment and subsequent development of the Chevalier Jackson Bronchoscopic Clinic of Temple University Hospital and Medical School. Here, his son, Chevalier L. Jackson, joined him in the clinical work and teaching program in broncho-esophagology and laryngeal surgery. The quiet, friendly guidance, the teaching of technical skill and medical judgment and finally the transfer of authority from one generation to the next was one of the ways in which the character and wisdom of this great man were most beautifully revealed. Under the son's guidance, the father's work continues.

In all medical achievements the beginning can never be defined—nor the end envisioned. Chevalier Jackson's influence in medicine will continue to be felt far beyond the borders of his country and the span of his life. Modern medicine as well as his individual patients pay great homage to this man who did so much more than his part "as his turn came 'round."

Paul H. Holinger, M.D., F.C.C.P., Chicago, Illinois

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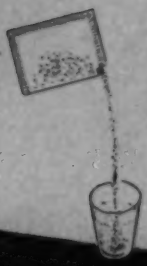

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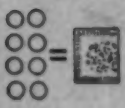

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